FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY

COMMITTEE (EMDAC)

Tuesday, July 19, 2011

8:00 a.m. to 5:00 p.m.

Hilton Washington DC/Silver Spring

Silver Spring, Maryland

Meeting Roster

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY

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5 Endocrinology, Diabetes and Hypertension Division

6 Vice Chair for Faculty Development

7 Department of Medicine

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9 Boston, Massachusetts

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11 **David M. Capuzzi, M.D., Ph.D.**

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13 Thomas Jefferson University &

14 Lankenau Institute for Medical Research

15 Philadelphia, Pennsylvania

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17 **Edward W. Gregg, Ph.D.**

18 Chief, Epidemiology and Statistics Branch

19 Division of Diabetes Translation

20 Centers for Disease Control and Prevention

21 Atlanta, Georgia

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1   **Ida L. Spruill, Ph.D., R.N.**

2   *(Consumer Representative)*

3   Assistant Professor

4   Medical University of South Carolina

5   College of Nursing

6   Charleston, South Carolina

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8   ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY

9   COMMITTEE MEMBER (Non-Voting)

10 **Enrico P. Veltri, M.D.**

11 *(Industry Representative)*

12 Vice President, U.S. Medical Affairs

13 Cardiovascular/Thrombosis

14 Sanofi-Aventis, U.S.

15 Bridgewater, New Jersey

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17 TEMPORARY MEMBERS (Voting)

18 **Ed J. Hendricks, M.D.**

19 Medical Director

20 Center for Weight Management

21 Roseville and Sacramento, California

22

1 **Sanjay Kaul, M.D.**

2 Director and Professor

3 Fellowship Training Program in

4 Cardiovascular Diseases

5 David Geffen School of Medicine at UCLA

6 Division of Cardiology

7 Cedars-Sinai Medical Center

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10 **Kevin D. McBryde, M.D.**

11 Program Director, Pediatric Nephrology

12 Office of Minority Health Research Coordination

13 National Institute of Diabetes and Digestive and

14 Kidney Diseases (NIDDK)

15 National Institutes of Health (NIH)

16 Bethesda, Maryland

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18 **Cassandra McIntyre**

19 *(Patient Representative)*

20 Mitchellville, Maryland

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2   Associate Professor of Medicine

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7   Burlington, Vermont

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9   **Abraham Thomas, M.D., M.P.H.**

10   *(Acting Chair)*

11   Division Head

12   Endocrinology, Diabetes, Bone, and Mineral

13   Disorders, Hypertension, Henry Ford Hospital

14   Whitehouse Chair of Endocrinology

15   Detroit, Michigan

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1   FDA PARTICIPANTS (Non-Voting)

2   **Curtis J. Rosebraugh, M.D., M.P.H.**

3   Director

4   Office of Drug Evaluation (ODE) II

5   Office of New Drugs (OND)

6   Center for Drug Evaluation and Research (CDER)

7   Food and Drug Administration (FDA)

8

9   **Mary H. Parks, M.D.**

10   Director

11   Division of Metabolism and Endocrinology

12   Products (DMEP)

13   ODE II, OND, CDER, FDA

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15   **Mark Avigan, M.D., C.M.**

16   Associate Director

17   Office of Surveillance and Epidemiology (OSE)

18   CDER, FDA

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20   **Ilan Irony, M.D.**

21   Diabetes Clinical Team Leader

22   DMEP, ODE II, OND, CDER, FDA

1   **Somya V. Dunn, M.D.**

2   Clinical Reviewer

3   DMEP, ODE II, OND, CDER, FDA

4

5   **Paul Tran, R.Ph.**

6   Designated Federal Officer, EMDAC

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C O N T E N T S

C O N T E N T S (continued)

1   P R O C E E D I N G S

2   (8:02 a.m.)

3   **Call to Order and Introduction**

4   DR. THOMAS: Good morning. I would first

5   like to remind everyone present to please silence

6   your cell phones, Blackberrys, and other devices if

7   you've not already done so. I'd also like to

8   identify the FDA press contact, Ms. Karen Riley.

9   If you're here, please stand.

10   Good morning. My name is Abraham Thomas.

11   I'm the acting chair of the Endocrinologic and

12   Metabolic Drugs Advisory Committee. I will now

13   call the meeting of the Endocrinologic and

14   Metabolic Drugs Advisory Committee to order. We

15   will go around the room, and please introduce

16   yourself. We'll start with the FDA and Dr. Curtis

17   Rosebraugh to my left and go around the table.

18   DR. ROSEBRAUGH: Curt Rosebraugh, director,

19   Office of Drug Evaluation II.

20   DR. PARKS: Mary Parks, director, Division

21   of Metabolism and Endocrinology Products.

22   DR. IRONY: Ilan Irony, clinical team leader

in diabetes.

DR. DUNN: Somya Dunn, clinical reviewer, diabetes.

DR. SEELY: Ellen Seely, Brigham and Women's Hospital, Harvard Medical School.

DR. SAVAGE: Peter Savage, NIDDK, NIH.

DR. FELNER: Eric Felner, associate professor of pediatrics, Emory University.

DR. CAPUZZI: David Capuzzi, professor of medicine biochemistry, Thomas Jefferson University in Philadelphia.

DR. BRITTAIN: Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases.

DR. THOMAS: Abraham Thomas, endocrinology, Henry Ford Hospital, Detroit, Michigan.

DR. TRAN: Paul Tran, the DFO for the Endocrinologic and Metabolic Drugs Advisory Committee.

DR. GREGG: Ed Gregg from the diabetes division at CDC in Atlanta.

DR. SPRUILL: I'm Ida Spruill, assistant

1   professor at the Medical University of South

2   Carolina, Charleston, South Carolina.

3   DR. PIANTADOSI: My name is Steve

4   Piantadosi. I'm professor of medicine and

5   biostatistics at Cedars Sinai Medical Center and

6   UCLA.

7   DR. STRADER: Doris Strader, associate

8   professor of medicine, Division of Gastroenterology

9   and Hepatology, University of Vermont.

10   MS. MCINTYRE: Cassandra McIntyre, patient

11   representative.

12   DR. KAUL: Good morning. Sanjay Kaul. I'm

13   a cardiologist at Cedars Sinai Medical Center at

14   UCLA.

15   DR. SMITH: Terry Smith, departments of

16   ophthalmology and internal medicine, University of

17   Michigan Ann Arbor.

18   DR. HENDRICKS: Ed Hendricks, Center for

19   Weight Management, Sacramento, California.

20   DR. VELTRI: Rick Veltri, medical affairs,

21   Sanofi, industry representative.

22   DR. THOMAS: For topics such as those being

1   discussed at today's meeting, there are often a

2   variety of opinions, some of which are quite

3   strongly held. One goal is that today's meeting

4   will be a fair and open forum for discussion of

5   these issues and that individuals can express their

6   views without interruption. Thus, as a gentle

7   reminder, individuals will be allowed to speak into

8   the record if only recognized by the chair. We

9   look forward to a productive meeting.

10   In the spirit of the Federal Advisory

11   Committee Act and the Government in the Sunshine

12   Act, we ask that the advisory committee members

13   take care that their conversations about the topic

14   at hand take place in the open forum of the

15   meeting.

16   We are aware that members of the media are

17   anxious to speak with the FDA about these

18   proceedings. However, FDA will refrain from

19   discussing the details of this meeting with the

20   media until its conclusion. Also, the committee is

21   reminded to please refrain from discussing the

22   meeting topics during breaks or lunch. Thank you.

Conflict of Interest Statement

DR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drug Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to, those found at 18 U.S.C., Section 208 and Section 712 of the Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committee are in compliance with the federal ethics and conflict of interest laws.

1   Under 18 U.S.C., Section 208, Congress has

2   authorized FDA to grant waivers to special

3   government employees and regular federal employees

4   who have potential financial conflicts when it is

5   determined that the agency's need for a particular

6   individual's services outweighs his or her

7   potential financial conflict of interest. Under

8   Section 712 of the federal Food, Drug, and Cosmetic

9   Act, Congress has authorized FDA to grant waivers

10   to special government employees and regular federal

11   employees with potential financial conflicts, when

12   necessary, to afford the committee essential

13   expertise.

14   Related to the discussion of today's

15   meeting, members and temporary voting members of

16   this committee have been screened for potential

17   financial conflicts of interest of their own, as

18   well as those imputed to them, including those of

19   their spouses or minor children, and, for purposes

20   of 18 U.S.C. Section 208, their employers. These

21   interests may include investments, consulting,

22   expert witness testimony, contracts, grants,

1   CRADAs, teaching, speaking, writing, patents and

2   royalties, and primary employment.

3   Today's agenda involves new drug application

4   NDA 202293, dapagliflozin, manufactured by Bristol-

5   Myers Squibb and AstraZeneca. Dapagliflozin is the

6   first drug in the class of sodium glucose

7   co-transporter 2 inhibitors, developed as an

8   adjunct to diet and exercise to improve glycemic

9   control in adults with type II diabetes mellitus.

10   This is a particular matters meeting, during

11   which specific matters related to dapagliflozin

12   will be discussed. Based on the agenda for today's

13   meeting and all financial interests reported by the

14   committee members and temporary voting members, a

15   conflict of interest waiver has been issued in

16   accordance to 18 U.S.C. Section 208(b)(3) to

17   Dr. Abraham Thomas.

18   Dr. Thomas's waiver, under 18 U.S.C. Section

19   208, is for a research grant to his employer,

20   funded by a competing firm. Dr. Thomas has no

21   personal involvement in the studies. The funding

22   for one study is between $0 to $50,000, and the

1   funding for the other is between $50,001 to

2    $100,000. The waiver allows the individual to

3   participate fully in today's deliberation. FDA's

4   reasons for issuing the waiver are described in the

5   waiver document, which is posted on the FDA website

6   at www.FDA.gov/advisorycommittee/advisorycommittee

7   meetingmaterialsdrug/default.htm.

8   Copies of the waivers may also be obtained

9   by submitting a written request to the agency's

10   Freedom of Information office at 12420 Parklawn

11   Drive, ELEM-1029, Rockville, Maryland 20857, or by

12   fax to (301)827-9267.

13   A copy of this statement will be available

14   for review at the registration table during this

15   meeting and will be included as part of the

16   official transcript.

17   To ensure transparency, we encourage all

18   standing members and temporary voting members to

19   disclose any public statement that they may have

20   made concerning the product at issue. With respect

21   to the FDA-invited industry representative, we

22   would like to disclose that Dr. Enrico Veltri is

1 participating in this meeting as a non-voting

2 industry representative acting on behalf of

3 regulated industry. Dr. Veltri's role at this

4 meeting is to represent industry in general and not

5 any particular company. Dr. Veltri is employed by

6 Sanofi-Aventis.

7   We would like to remind members and

8 temporary voting members that if the discussion

9 involves any other product or firm not already on

10 the agenda, for which the FDA participant has a

11 personal or imputed financial interest, the

12 participants need to exclude themselves from such

13 involvement, and their exclusion will be noted for

14 the record. FDA encourages all other participants

15 to advise the committee of any financial

16 relationship that they may have with the firm at

17 issue. Thank you.

18   DR. THOMAS: Before we start the morning's

19 proceedings, I'd like to invite Dr. Mary Parks to

20 come up for a special presentation.

21   DR. PARKS: Good morning. Thank you,

22 Dr. Thomas, for allowing me a few minutes here to

1   acknowledge a member of our advisory committee who

2   will be completing his term this fall.

3   Dr. Rick Veltri joined EMDAC as our industry

4   representative in June of 2008. During his term,

5   he has participated in at least 10 advisory

6   committee meetings, some of them very

7   controversial, including his first one, which was

8   to discuss whether or not companies developing

9   therapies for type II diabetes should be required

10   to conduct a dedicated cardiovascular risk

11   assessment of the therapy.

12   Dr. Veltri completed his cardiology training

13   at Johns Hopkins and went on for at least 15 plus,

14   if not 20 plus, years of experience in the

15   pharmaceutical industry. As an industry

16   representative, he is a non-voting member of this

17   committee. However, he has contributed extensively

18   to the discussion of all of these meetings. He's

19   also asked a lot of critical and thought-provoking

20   questions to both FDA and the sponsor.

21   On behalf of the FDA, I would like to thank

22   Dr. Veltri for his contributions to the advisory

1   committee process.

2   Dr. Veltri, if you could please come to the

3   podium, I'd like to present to you this plaque,

4   commemorating your three years of dedication and

5   service to the Endocrine and Metabolism Drugs

6   Advisory Committee.

7   [Applause.]

8   DR. VELTRI: Thank you, Mary. Thank you.

9   DR. THOMAS: We will now proceed with the

10   FDA opening remarks from Dr. Ilan Irony. I'd like

11   to remind public observers at this meeting that

12   while this meeting is open for public observation,

13   public attendees may not participate except at the

14   specific request of the panel.

15   **Introduction/Background**

16   DR. IRONY: Good morning. My name is Ilan

17   Irony, and I'm a clinical team leader on diabetes.

18   I want to welcome everybody to this advisory

19   committee meeting and thank Dr. Thomas and the

20   panel members for their participation here today,

21   and also the public, and particularly those

22   speaking in the public hearing session this

1   afternoon.   Today, we are here to discuss the new

2   drug application for dapagliflozin.

3   Here's an outline of my brief presentation

4   today.   I'm going to talk about dapagliflozin as an

5   introduction, the agenda for today's meeting, the

6   particular topics that we selected for discussion

7   for the panel members, and, finally, the voting

8   questions for today.

9   So dapagliflozin is a first-in-class new

10   molecular entity drug indicated for the treatment

11   of adults with type II diabetes. Dapagliflozin is

12   a selective inhibitor of the sodium glucose

13   co-transporter 2, or SGLT2. The natural model, the

14   mechanism of action that this drug is based, is

15   designated as familial renal glucosuria, which is

16   caused by a mutation mostly from the coding chain

17   of SGLT2.

18   The few cases reported for this rare

19   disorder have a benign course. The effect of

20   dapagliflozin on glycemia is independent of insulin

21   secretion and independent of insulin sensitivity.

22   Its effect is dependent on plasma glucose

1   concentration and glomerular filtration rate.

2   So for today's agenda, this morning, you're

3   going to hear from the applicant followed by the

4   FDA presentations. And each of those will be

5   followed by a brief period of clarifying questions

6   directed to the applicant or to the FDA.

7   After lunch, we're going to have the open

8   public hearing session, and this will be followed

9   by a discussion among the panel members, and FDA,

10   and the applicant, of selected issues, and finally

11   the questions that will complete the rest of the

12   day. And, hopefully, we'll finish before 5:00.

13   So I'm going to start the topics for

14   discussion today with -- my next two slides are

15   about efficacy. As I mentioned before, the effect

16   of dapagliflozin depends on glomerular filtration

17   rate, or GFR. As GFR declines along with the

18   progression of type II diabetes, so does the

19   efficacy of dapagliflozin.

20   The applicant did a dedicated study in

21   patients with moderate renal impairment, and those

22   were classified as having an estimated GFR between

1   30 and 59 milliliters per minute per 1.73 meters of

2   body surface area. The primary endpoint for this

3   trial was a placebo-adjusted change in hemoglobin

4   A1c from baseline to week 24, and the trial was

5   continuing to week 52. As you can see from the

6   bottom two bullets, there was not much change in

7   hemoglobin A1c for either dose, dapagliflozin,

8   5 milligrams daily, or dapagliflozin, 10 milligrams

9   daily.

10   So we want the panel members to discuss

11   implications of this reduced efficacy in type II

12   diabetes, where renal impairment can impact a

13   sizeable proportion of individuals with this

14   disease. We also want you to discuss whether

15   additional studies should be conducted to better

16   characterize the efficacy of dapagliflozin in

17   type II diabetes, or whether monitoring for renal

18   function should be performed prior to and/or during

19   treatment with dapagliflozin.

20   Next, we're going to move to topics of

21   safety. In the next four slides, we'll briefly

22   present those to you. We'll start with liver

1   safety.

2   So five patients treated with dapagliflozin

3   in the large phase 2b/phase 3 safety pool were

4   detected as having either an ALT or AST, or both,

5   greater than five times the upper limit of normal,

6   accompanied or followed by a total bilirubin

7   greater than two times the upper limit of normal.

8   This meets the biochemical criteria for Hy's law.

9   An adequate explanation for these biochemical

10   abnormalities was identified in all but one case.

11   That one case was deemed as a probable case of

12   drug-induced liver injury.

13   It's important to note that no overall

14   imbalances in severe, meaning greater than five

15   times the upper limit of normal or greater than 10

16   times the upper limit of normal, in hepatic

17   aminotransferases were detected in the

18   dapagliflozin clinical program. In addition, no

19   signal for hepatotoxicity was detected in the non-

20   clinical program.

21   So we would like the committee members to

22   discuss and comment on the clinical relevance of

1   this one case of potential Hy's law and whether

2   sufficient evaluation has been conducted pre-

3   marketing to determine if dapagliflozin is

4   associated with the risk of hepatotoxicity.

5   We'll now switch to the topic of cancer. So

6   numeric imbalances in both breast and bladder

7   cancer were observed in the clinical development

8   program. Again, in the large phase 2b and phase 3

9   safety pool, 9 patients treated with dapagliflozin,

10   9 female patients, were diagnosed with breast

11   cancer, versus one patient in the control groups.

12   With regard to bladder cancer, 9 male

13   patients treated with dapagliflozin were diagnosed

14   with bladder cancer, versus one patient in the

15   control group. In the brackets, you can see also

16   the incidence rates, comparing those cases to

17   exposure.

18   So those cases, among dapagliflozin-treated

19   subjects, were not only compared to controls, but

20   they were compared to what would be expected in the

21   U.S. population of diabetics with cancer. And the

22   comparator here is the Surveillance Epidemiology

1   and End Results database of the National Cancer

2   Institute, adjusted for the higher incidence of

3   those cancers, breast and bladder cancer, in

4   diabetics, based on some appropriate literature

5   references.

6   So we want you to discuss today, for both

7   types of cancer, whether these imbalances in the

8   clinical program signify a risk of carcinogenic

9   potential associated with dapagliflozin. And for

10   both types of cancer, we want you to comment

11   whether these numeric imbalances were impacted by

12   any imbalances of baseline risk factors or any

13   detection bias.

14   In addition to the topics of cancer and

15   liver safety, we want you to discuss also the

16   clinical significance of the following in type II

17   diabetes: an increase in genital urinary

18   infections with dapagliflozin and any long-term

19   consequences of this; bone safety concerns; any

20   other safety issues identified in the pre-marketing

21   application.

22   Finally, the voting question, which is the

following: Do the efficacy and safety data provide

substantial evidence to support approval of

dapagliflozin as an adjunct to diet and exercise to

improve glycemic control in adults with type II

diabetes? We want you to vote, please, yes or no.

To follow up on that voting question, if you

voted yes, do you recommend any further data be

obtained post-marketing? If you voted no, what

further data should be obtained?

Again, I want to thank the committee

members, and particularly Dr. Thomas for chairing

the panel, and for preparing this thorough

discussion of the topics today. Thank you.

DR. THOMAS: Because of today's road

closure, some committee members may be arriving

late. If we could have Dr. Avigan and Dr. Savage

introduce themselves for the record.

DR. AVIGAN: That was exactly right. There

was a road closure. Mark Avigan, FDA, Office of

Surveillance and Epidemiology.

DR. SAVAGE: Yes, I introduced myself before

I got here, just as you started, but I'm from the

1   Diabetes Institute at the NIH. I'm an

2   endocrinologist.

3   DR. THOMAS: My fault.

4   We will now proceed with the sponsor's

5   presentations. I'd like to remind public observers

6   at this meeting that while this meeting is open for

7   public observations, public attendees may not

8   participate except at the specific request of the

9   panel.

10   Both the Food and Drug Administration and

11   the public believe in a transparent process for

12   information gathering and decision making. To

13   ensure such transparency at the advisory committee

14   meeting, FDA believes that it is important to

15   understand the context of an individual's

16   presentation.

17   For this reason, FDA encourages all

18   participants, including the sponsor's non-employee

19   presenters, to advise the committee of any

20   financial relationships that they may have with the

21   firm at issue, such as consulting fees, travel

22   expenses, honoraria, and interest in the sponsor,

1   including equity interest and those based upon your

2   outcome of the meeting.

3   Likewise, FDA encourages you, at the

4   beginning of your presentation, to advise the

5   committee if you do not have any such financial

6   relationships. If you choose not to address this

7   issue of financial relationships at the beginning

8   of your presentation, it will not preclude you from

9   speaking.

10   At this time, I would like to invite the

11   sponsor to start their presentation.

12   **Sponsor Presentation – Amy Jennings**

13   DR. JENNINGS: Thank you, Chairman Thomas.

14   Good morning, ladies, and gentlemen, and

15   members of the Endocrine and Metabolic Advisory

16   Committee. I am Amy Jennings, director and U.S.

17   regulatory lead for dapagliflozin at Bristol-Myers

18   Squibb. Bristol-Myers Squibb and AstraZeneca are

19   pleased to be here today to present data

20   demonstrating that dapagliflozin is an important

21   and needed treatment option for patients with

22   type II diabetes.

1   Dapagliflozin is an oral active inhibitor of

2   the sodium glucose co-transporter number 2. This

3   new mechanism of action acts in the kidney,

4   employing the kidney's natural ability to excrete

5   glucose out in the urine. Unlike many other

6   currently available anti-diabetic agents,

7   dapagliflozin has a direct approach to glucose

8   management and has demonstrated improvements in

9   glycemic control, along with the added benefit of

10   modest weight loss.

11   Our proposed indication for dapagliflozin is

12   for the use as an adjunct therapy to diet and

13   exercise to improve glycemic control in patients

14   with type II diabetes when used as either

15   monotherapy or as add-on combination therapy to

16   other oral anti-diabetic agents, or when added onto

17   insulin.

18   For our presentations today, Dr. John Buse,

19   director of the Diabetes Care Center at the

20   University of North Carolina, and a past president

21   of the American Diabetes Association, will begin by

22   providing an overview of the current landscape of

1   anti-diabetic agents. He will also discuss the

2   need for additional therapies to treat patients

3   with type II diabetes.

4   Dr. Elizabeth Svanberg, the development lead

5   for dapagliflozin at Bristol-Myers Squibb, will

6   then provide an overview of the dapagliflozin

7   development program, which was robust, with

8   approximately 6,000 subjects being evaluated in 41

9   clinical trials.

10   Dr. Shamik Parikh and Dr. Jim List from

11   AstraZeneca, the two medical leads for the

12   dapagliflozin program, will then describe the

13   efficacy and safety data of dapagliflozin,

14   respectively.

15   Dr. Jim Gavin, CEO and chief medical officer

16   of Healing our Village, will then translate these

17   benefits and risks of dapagliflozin to diabetic

18   patients seen in clinical practice.

19   Dr. Brian Daniels, head of development and

20   medical affairs at Bristol-Myers Squibb, will then

21   conclude our presentation by describing our

22   commitment to continue to assess the

characteristics of dapagliflozin in the post-
approval setting.

Today, we also have several experts to
assist us in answering any questions that you may
have.

I'd now like to introduce Dr. John Buse to
provide an overview of the current landscape of
anti-diabetic agents. Thank you.

Sponsor Presentation - John Buse

DR. BUSE: Good morning. Chairman Thomas
and members of the advisory committee, thank you
for the opportunity to speak to you regarding the
unmet needs in diabetes care. As a matter of
disclosure, the sponsor is contracted with my
employer for my services as a consultant; however,
I do not derive personal financial benefit from
this relationship.

I've worked in the field of diabetes for
25 years, dividing my time about equally between
clinical care, clinical research, teaching, and
administration. I'm currently the chief of the
Division of Endocrinology, director of the Diabetes

1   Care Center, and executive associate dean for

2   clinical research at the University of North

3   Carolina School of Medicine. I recently served as

4   president for medicine and science at the American

5   Diabetes Association.

6   Over the last 10 to 15 years, we've made

7   tremendous advances in diabetes care in the United

8   States, from strengthening clinical guidelines and

9   increasing public awareness, to improving diagnoses

10   and treatment as a result of specific disease

11   management programs, improved screening, better

12   access to diabetes education and supplies, and new

13   pharmacologic agents.

14   As a result, the proportion of patients who

15   achieve the general glycemic target of an A1c of

16   less than 7 percent, suggested by the American

17   Diabetes Association, has improved to over

18   50 percent. And not shown here, the incidence rate

19   of most diabetes complications seem to be falling.

20   Nevertheless, the burden of diabetes continues to

21   increase, fueled by the epidemic of diabetes.

22   Let me share some numbers with you from the

1   Centers for Disease Control and Prevention's 2011

2   National Diabetes fact sheet. Diabetes now affects

3   about 26 million Americans, over 8 percent of the

4   population, with nearly 2 million new diagnoses a

5   year. Despite $174 billion in total costs for

6   diabetes, the risk for death among people with

7   diabetes is about twice that of people of similar

8   age, but without diabetes, with upwards of

9   70 percent of these deaths related to

10   cardiovascular diseases. Over 4 million people

11   with diabetes have diabetic eye disease, and

12   655,000 have advanced diabetic retinopathy that

13   could lead to severe vision loss.

14   In 2008, over 200,000 people with diabetes

15   lived with end-stage renal disease on chronic

16   dialysis or with a kidney transplant, and almost

17   50,000 people with diabetes began treatment for

18   end-stage kidney disease. Over 65,000 non-

19   traumatic, lower-limb amputations are performed

20   annually in people with diabetes. Parenthetically,

21   it should be noted that less than 10 percent of the

22   cost of diabetes is related to diabetes drug

1   therapy.

2   How could it be that, despite our advances

3   and our investment in diabetes care, almost

4   50 percent of Americans with diabetes still are

5   inadequately controlled, as determined by A1c, and

6   still suffer such a heavy burden of disabling

7   complications and early death.

8   Here, you see an illustration of the natural

9   history of diabetes. Most patients progress from

10   improved control after initiation of a drug therapy

11   to loss of control over a period of five years

12   after initiating a particular anti-hyperglycemic

13   agent, and then inexorably progress from

14   monotherapy to combination therapy. Therefore,

15   many patients require two, three, or even more

16   anti-hyperglycemic therapies.

17   Depending on how you count them, we have

18   over a dozen different types of diabetes

19   medications on the market. In this slide, I've

20   color-coded a number of characteristics of each of

21   these agents, with green for good, and red for

22   potentially undesirable, with yellow being

1   intermediate.

2   As you can see, except for metformin,

3   essentially all of the available agents, except for

4   some recent additions near the bottom of the slide,

5   are associated with hypoglycemia, weight gain, or

6   are viewed by many as difficult to take, either

7   related to dosing frequency or the need for

8   injection. Some of the newer agents only have

9   modest efficacy.

10   As noted here, many agents are associated

11   with safety concerns, particularly newer agents,

12   where inadequate experience makes it difficult for

13   many practitioners to put these safety issues in

14   perspective. As a result, there are no absolutely

15   clear broadly-accepted choices for the ideal

16   treatment path beyond metformin for the average

17   patient with diabetes.

18   That said, it's important to put these

19   safety issues in perspective, as was nicely done in

20   a recent review by Dr. Rich Bergenstal, the

21   immediate past president of the American Diabetes

22   Association, Dr. Cliff Bailey, the EESD

1   representative on the European Medicines Agency,

2   and Dr. David Kendall, the chief science and

3   medical officer of the American Diabetes

4   Association.

5   In green, it is known that important adverse

6   events associated with current treatments are

7   relatively common, affecting up to about 1 percent

8   of those treated. However, these agents remain

9   important parts of our treatment protocols, as

10   these harms are more than balanced in white, with

11   benefits important to patients, as demonstrated in

12   the UKPDS study.

13   As noted in red, cardiovascular

14   complications, as well as disabling microvascular

15   complications, remain common in type II diabetes,

16   despite treatment. That is fundamentally the unmet

17   need in diabetes management, the need to minimize

18   the burdens of disability and early death in

19   patients with type II diabetes.

20   I believe that dapagliflozin addresses these

21   unmet needs nicely in comparison to the other

22   available treatments. Dapagliflozin has a novel

1   mechanism of action, independent of circulating

2   insulin levels. It is associated with good

3   efficacy and lowering A1c, equivalent to

4   sulfonylurea or metformin.

5   Dapagliflozin is not associated with an

6   intrinsic risk of hypoglycemia. It is associated

7   with moderate weight loss. It is easy and

8   convenient to take, a single-dose strength for most

9   patients, taken orally once a day, irrespective of

10   the timing of meals.

11   Dapagliflozin is effective in a broad

12   spectrum of patients with type II diabetes,

13   independent of background therapy or duration of

14   disease. And, finally, the safety concerns raised

15   in the briefing materials seem modest on par with

16   the other available agents and addressable through

17   patient selection, counseling, and further study.

18   Thank you. Dr. Svanberg will now introduce

19   the dapagliflozin program.

20   **Sponsor Presentation – Elisabeth Svanberg**

21   DR. SVANBERG: Thank you, Dr. Buse.

22   Mr. Chairman, members of the advisory

1   committee, members of FDA, ladies and gentlemen,

2   good morning. My name is Elizabeth Svanberg, and

3   I'm the development leader for dapagliflozin at

4   Bristol-Myers Squibb.

5   Current diabetes treatment work across

6   various organs and most of them work dependently on

7   insulin. Today's presentation focuses on SGLT2,

8   which is the main transporter for renal glucose

9   reabsorption from the glomerular filtrate. SGLT2

10   is almost exclusively expressed in the kidney.

11   Glucose is filtered through the glomerulus.

12   It is reabsorbed through SGLT2, which is located in

13   the proximal tubule. And it brings glucose back

14   into the systemic circulation. When SGLT2 is

15   inhibited, less glucose is reabsorbed and more

16   pronounced glucosuria appear.

17   Glucosuria is an easily and readily measured

18   pharmacodynamic marker of SGLT2 inhibition. The

19   direct excretion of glucose and the associated

20   excess calories may suggest a way to control

21   weight, and it may be a reason for patients to

22   adhere to and comply with treatment.

1   Effects of SGLT2, as a mode of action,

2   include both benefits and risks. The benefits are

3   the insulin-independent mode of action that makes

4   SGLT2 inhibition complementary to currently

5   available treatments. The glycemic control, which

6   includes HbA1c lowering as well as reduction in

7   fasting plasma glucose and post-prandial glucose,

8   the excretion of glucose calories leads to the

9   weight loss. And together with the glucose

10   excretion goes salt and water, a diuretic effect

11   that may translate into blood pressure reduction.

12   Blood pressure effects with SGLT2 inhibition is

13   evaluated specifically in a dedicated phase 3

14   program.

15   Risks include hypoglycemia, as well as

16   effects on renal function, as the kidney is the

17   target organ. The diuretic effects could imply

18   effects such as hypovolemia, hypotension, and

19   dehydration. It may also affect bone mineral

20   metabolism.

21   The glucose in the urine may serve as a

22   nutrient for bacteria and other pathogens. And

1   urinary tract infections vulvovaginitis and

2   balanitis may be risks with treatment.

3   All these parameters were thoroughly

4   evaluated in the dapagliflozin development program.

5   SGLT2 inhibition, as a therapeutic approach, stems

6   from lessons in nature. The use of phlorizin from

7   the apple bark was described to lead to glucosuria

8   already more than 100 years ago. Human SGLT2

9   mutation results in a condition called familial

10   renal glucosuria, a rare, natural benign phenotype

11   characterized by lifelong glucosuria.

12   The amount of glucose excreted depends on

13   the mutation, and the most severe one is the sero

14   mutation, sero because there is no reabsorption in

15   the kidney. As far as is known and

16   described -- and this is a very rare

17   condition -- the condition, nonetheless, is

18   compatible with a long life.

19   The SGLT2 program utilized these findings to

20   rationally design a reversible inhibitor with the

21   potency at the low nanomolar level with high

22   selectivity and an oral bioavailability, which

1   resulted in the advancement of dapagliflozin as a

2   therapeutic candidate.

3   For the ease of the presentation and for the

4   discussion, may I suggest that we call

5   dapagliflozin dapa? And we will use the terms

6   dapagliflozin and dapa interchangeably throughout

7   our presentation.

8   I will briefly summarize the clinical

9   pharmacology program. Dapa was evaluated in 27

10   pharmacology studies in healthy volunteers, in

11   patients with renal impairment, and in patients

12   with hepatic impairment, as well as in subjects

13   with type II diabetes.

14   We explored a wide range of doses, from one

15   microgram to 500 milligrams. In these studies,

16   dapa was found to be safe and well tolerated, up to

17   50 times the proposed normal dose. No dose-

18   limiting toxicity was observed.

19   Dapagliflozin's pharmacodynamic effects are

20   readily measured by glucose excretion in the urine.

21   This is observed already after a single dose. The

22   proposed usual daily dose of 10 milligrams provides

1   75 percent of the maximum effect, and that is

2   consistent with dapa's high potency.

3   The most known effect on QTc interval or

4   heart rate; dapa was readily and extensively

5   absorbed, and it may be given without regards to

6   means. There's no dose adjustment needed due to

7   pharmacokinetic properties. Since dapa is not

8   metabolized through the CYP pathway, it has a low

9   potential for clinically meaningful drug-drug

10   interactions. Taken together, that makes dapa an

11   easy drug to use.

12   The phase 2b program evaluated doses, 2.5 to

13   50 milligrams over 12 weeks in treatment-naive type

14   II diabetic subjects. As expected, due to the mode

15   of action, an increase in urinary glucose excretion

16   was seen.

17   The clinically meaningful endpoint of a

18   reduction in HbA1c was also measured. And taken

19   together, these data suggest that dapa's

20   therapeutic effect is achieved at a 10-milligram

21   dose with no or little effect at a higher dose.

22   The doses do progress from phase 2b to

1   phase 3 were therefore selected to be 2.5, 5, and

2   10 milligrams.

3   Altogether, the dapagliflozin program was

4   truly global in nature. The program consisted of

5   6,000 patients, and it spanned 14 phase 2b and

6   phase 3 studies. The patients were ranging across

7   stages of disease from treatment-naive to

8   treatment-experienced patients with several years-

9   long, decade-long disease. It was designed to

10   thoroughly describe the effects of a novel,

11   therapeutic class with a unique mode of action.

12   The dapagliflozin phase 3 program, to the

13   left, are six placebo-controlled trials that

14   evaluated dapagliflozin across the spectrum of

15   disease, from drug-naive patients with newly onset

16   disease in the monotherapy studies to those with

17   inadequate glycemic control on a background of

18   various anti-diabetic treatment, including insulin

19   therapy.

20   In the middle are three trials using an

21   active comparator. These trials included a head-

22   to-head study of dapagliflozin versus SU in

1 patients who were inadequately controlled on

2 metformin. Two studies evaluated the initial

3 combination of dapagliflozin together with

4 metformin in treatment-naive patients who had poor

5 glycemic control. And it compared the combination

6 to the single treatment arms respectively. One of

7 these studies included a direct comparison of dapa

8 versus metformin, a single-agent treatment.

9   To the right are two specialty studies, one

10 for evaluation of body weight and body composition,

11 and the other, a specifically-designed study

12 conducted in type II diabetic patients with

13 moderate renal impairment.

14   I will now hand over to Dr. Parikh for

15 presentation of dapa efficacy in phase 3. And when

16 we have completed our presentation, I will return

17 to the podium to moderate the question-and-answer

18 session. Thank you.

19   **Sponsor Presentation – Shamik Parikh**

20   DR. PARIKH: Thank you, Dr. Svanberg.

21   Good morning. The short-term and long-term

22 data from our phase 3 studies illustrate

1 dapagliflozin's consistent and sustained efficacy

2 in a broad range of patients with type II diabetes,

3 irrespective of their background regimens.

4 Starting with trial design, our phase 3

5 studies were designed in a similar pattern with

6 enrollment period followed, in most studies, by

7 leading or a dose-optimization period prior to

8 subject randomization.

9 The primary endpoint was evaluated at the

10 end of a short-term treatment period of 24 weeks in

11 all trials, with the exception of the head-to-head

12 study versus sulfonylurea, where it was evaluated

13 at one year. Eight of the 11 phase 3 studies had

14 long-term extensions that were site- and subject-

15 blinded, and ranged for an additional six months to

16 three years.

17 Patients with type II diabetes and A1c

18 ranging from 6.5 to 12 percent were enrolled in

19 these studies, with the most common range allowed

20 being 7 to 10 percent. Renal function criteria

21 were influenced by the metformin label because

22 metformin was used as a background regimen or as a

1   glycemic rescue medication in these trials.

2   The program allowed for inclusion of

3   patients with a past history of urinary tract and

4   genital tract infections, but excluded patients who

5   are considered at risk of dehydration by the

6   investigator.

7   With regards to data analysis, analysis of

8   covariance, excluding data after glycemic rescue,

9   was used to assess the primary and all-continuous

10   secondary endpoints. Last observation carried

11   forward, or LOCF, approach was used when

12   measurements were not available. Sensitivity

13   analyses was conducted to support the conclusions

14   of the primary analysis. For efficacy assessments

15   in the long-term extension period, repeated

16   measures, mixed-model analysis was conducted using

17   observed cases without LOCF.

18   In phase 3, we evaluated short-term efficacy

19   with changes in A1c, fasting plus more glucose and

20   post-prandial glucose in placebo-controlled studies

21   at the 24-week time point. Due to caloric loss

22   associated with glucosuria, we evaluated change in

1   body weight as a secondary endpoint. We performed

2   active comparisons of dapagliflozin with commonly-

3   used oral anti-diabetic agents such as metformin

4   and glipizide.

5   We performed subgroup analysis of full data

6   to better understand the effects of different

7   baseline and disease characteristics on the A1c

8   lowering of dapagliflozin. And we conducted long-

9   term extensions to evaluate dapagliflozin's safety

10   and durability of efficacy.

11   In our phase 3 program, short-term efficacy

12   was evaluated in the six placebo-controlled trials,

13   consisting of two monotherapy and the four add-on

14   studies on a background of different anti-diabetic

15   agents. Each of these six trials was designed with

16   the primary objective of assessing A1c reduction

17   for dapa versus placebo at week 24. All six trials

18   met their primary endpoint.

19   Across these six individual studies, there

20   were consistent reductions in A1c with dapa

21   treatment. Mean baseline A1c ranged from

22   7.9 percent in the low dose monotherapy study on

1   the left to 8.5 percent on the add-onto-insulin

2   study towards the right. The 10-milligram dose,

3   represented by the yellow bars, were studied in

4   every trial, with the exception of the low dose

5   monotherapy study.

6   Three results are worth noting here. First,

7   dapagliflozin therapy led to a consistent reduction

8   in A1c in these six studies, irrespective of the

9   duration of diabetes or background therapy.

10 Second, there was a dose-dependent reduction in

11 A1c. The higher dose had a numerically better A1c

12 reduction than the lower dose in each of the six

13 studies.

14   Five of the studies evaluated the top two

15 doses, represented by the 5 milligrams shown in

16 green and the 10 milligrams shown in yellow, in a

17 parallel fashion. In each of these five studies,

18 the numerical A1c reduction was better at the

19 10-milligram dose than the 5-milligram dose.

20   The third point is about the magnitude of

21 A1c reduction. With the 10-milligram dose, there

22 was a statistically significant placebo-corrected

1   A1c reduction of 0.5 to 0.7 percent across the

2   studies. Overall, dapagliflozin had a consistent

3   and a dose-dependent effect with clinically

4   relevant A1c reductions at the 10-milligram dose in

5   a wide range of patients with type II diabetes.

6   Similar benefits were observed for fasting

7   plasma glucose. Change in fasting plasma glucose,

8   or FPG, was the secondary endpoint in these

9   studies. As for A1c, there was a consistent and

10   dose-dependent response for fasting plasma glucose.

11   FPG change, with the lower dose of 2.5 milligrams,

12   was not statistically significant in two studies.

13   At the top two doses, fasting plasma glucose

14   reductions were statistically significant compared

15   to placebo and numerically better at the

16   10-milligram than the 5-milligram dose.

17   In addition to fasting plasma glucose, post-

18   prandial glucose, or PPG, was also reduced with

19   dapagliflozin. Change in post-prandial glucose was

20   evaluated as a secondary endpoint in three studies,

21   as a mixed-meal tolerance test in the low dose

22   monotherapy study on the left and as an oral

1 glucose tolerance test in the two studies on the

2 right.

3   Dapa therapy reduced 2-hour post-prandial

4 glucose levels in all three studies. The magnitude

5 of post-prandial glucose lowering was greater than

6 that seen with fasting plasma glucose lowering.

7 Given dapa's mechanism of action, leading to

8 caloric loss by glucosuria, a decrease in body

9 weight was observed in our clinical studies.

10   Change in body weight was a secondary

11 endpoint in these trials. Over 90 percent of the

12 patients were overweight at baseline. A reduction

13 in body weight was observed with dapa treatment in

14 all clinical trials. In the pioglitazone add-on

15 studies, shown towards the right, dapa treatment

16 mitigated the weight gain that is associated with

17 biotherapy. Across the studies, dapagliflozin

18 treatment led to a placebo-corrected weight change

19 of 1 to 2 kilograms, or 2 to 4 pounds, over 24

20 weeks.

21   In order to better characterize this weight

22 loss effect, particularly the contribution of fat

1   loss to fluid loss, we conducted a dedicated

2   phase 3 study to evaluate changes in weight and

3   body composition that showed that weight loss was

4   primarily due to fat loss.

5   In this study, patients inadequately

6   controlled on stable metformin therapy were

7   randomized to dapagliflozin 10 milligrams or

8   placebo. The primary endpoint was change in body

9   weight at week 24.

10   As illustrated by the yellow line in the

11   graph, dapa, 10 milligrams per day, led to a

12   gradual reduction in body weight of 2.96 kilograms

13   from baseline that had not plateaued by week 24.

14   The difference of 2.1 kilograms between

15   dapagliflozin and placebo groups was statistically

16   significant.

17   Along with changes in weight, we assessed

18   changes in body composition with whole body dual

19   x-ray absorptiometry scans. These dexa scans

20   evaluated changes in fat mass and lean mass at

21   baseline and week 24.

22   There was a statistically significant

1   decrease in fat mass with dapa group compared to

2   placebo. Two-thirds of the weight loss in the dapa

3   group, shown in red, was due to fat loss. The

4   remaining one-third, shown in green, was due to

5   lean mass that consisted of the non-fat, non-bone

6   mass, including the fluid compartment.

7   In contrast, the placebo group demonstrated

8   similar changes in fat mass and lean mass. In

9   addition, visceral adipose tissue volume was also

10   examined, using MRI abdomen, in a subset of

11   patients and was decreased with dapa treatment.

12   The results from this study show that weight

13   loss observed with dapagliflozin is primarily

14   attributable to a reduction in body fat mass.

15   The benefits observed with dapa treatment in

16   placebo-controlled studies were replicated in

17   studies with active comparisons. The metformin

18   combination and comparison trial recruited drug-

19   naive patients with poorly controlled diabetes.

20   The mean A1c was just over 9 percent,

21   indicating that some of these patients already had

22   glucosuria at baseline. These patients were

1   randomized into one of three treatment groups: the

2   initial combination group that received metformin

3   XR, 2000 milligrams, and dapa, 10 milligrams, shown

4   in the yellow dashed line; the met XR monotherapy

5   group, shown in red; or the dapa, 10 milligrams,

6   monotherapy, shown in yellow.

7   There were two comparisons made. In the

8   first comparison, the combination of dapa with met

9   XR in the dashed line was compared to the two

10   monotherapies. The combination therapy reduced

11   mean A1c by approximately 2 percent from baseline.

12   That was significantly better compared to each

13   individual monotherapy.

14   The second comparison was a prespecified

15   test for non-inferiority between the two

16   monotherapies, between dapa 10 milligrams and

17   met XR 2,000 milligrams at week 24. Dapagliflozin

18   was non-inferior to metformin, with A1c reductions

19   of 1.45 and 1.44 percent, respectively. Also, in

20   the same study, dapa was superior to metformin in

21   reducing fasting plasma glucose and body weight.

22   We also compared dapagliflozin with the

1   sulfonylurea agent, glipizide, in a head-to-head

2   study, on a background of stable metformin therapy.

3   This non-inferiority study was designed and

4   conducted differently than other phase 3 trials.

5   Let me explain these differences before showing the

6   data.

7   The primary objective was to compare changes

8   in A1c at the 52-week time point. This was done

9   because the study consisted of two periods, an

10   18-week titration period followed by a 34-week

11   maintenance period.

12   Dapa and glipizide were both titrated up for

13   the first 18 weeks to the highest tolerated dose

14   level, up to 10 milligrams for dapa and up to

15   20 milligrams for glipizide, to achieve a fasting

16   plasma glucose of less than or equal to

17   110 milligrams per deciliter. At the end of the

18   18-week titration, A1c lowering with dapa, shown in

19   yellow, was less pronounced compared to glipizide,

20   shown in blue.

21   The titration period was followed by the

22   maintenance period when no further titrations were

1   allowed, except for any down titrations due to

2   hypoglycemia. During the maintenance period, the

3   maximum A1c lowering, achieved at week 26 in the

4   dapa group, was maintained until week 52.

5   In contrast, there was a rating of A1c

6   reduction with glipizide after the titration

7   period, a pattern that has also been observed in

8   other studies with sulfonylurea agents. At the end

9   of 52 weeks, both treatments had identical A1c

10   reduction of .52 percent that met the non-

11   inferiority criteria. An additional three-year

12   extension of this trial is currently ongoing that

13   would help us follow the trajectory of these A1c

14   reductions beyond one year.

15   The increased efficacy noted with glipizide

16   during the initial part of this study was also

17   associated with an increased risk of hypoglycemia.

18   By week 52, 41 percent of patients in the glipizide

19   group had at least one episode of hypoglycemia,

20   compared to 3.5 percent of patients in the dapa

21   group. Over 90 percent of these patients with

22   hypoglycemia had come from hypoglycemia with a

glucose level of less than 63 milligrams per deciliter.

Reductions in body weight observed in the placebo-controlled studies were also replicated in this active comparison study of a 52-week duration. Dapagliflozin led to weight loss, whereas glipizide led to weight gain, with a statistically significant difference of 4.6 kilograms between the two treatments. Proportion of patients with greater than or equal to 5 percent weight loss was considerably higher for dapa compared to glipizide. At week 52, one-third of all dapa-treated patients had a weight loss of greater or equal to 5 percent, compared to 2.5 percent of patients in the glipizide group.

In addition to analyzing data from individual trials, we performed subgroup analyses on the 24-week pool data from nine phase 3 studies. The only studies not represented in this pool were the head-to-head comparison to sulfonylurea because there was no problem comparison and the renal impairment study, because it was conducted in a

1   special population.

2   These subgroup analyses were done to assess

3   whether dapa's A1c lowering was modified by any

4   patient characteristics and baseline variables.

5   Within our dataset, no difference in efficacy was

6   detected with respect to gender, race, ethnicity,

7   region, baseline body mass index, or duration of

8   diabetes.

9   Interactions were detected for three

10   variables: baseline hemoglobin A1c, baseline

11   estimated glomerular filtration rate, or eGFR, and

12   age. As expected, based on dapa's mechanism of

13   action and as observed for other oral anti-diabetic

14   agents, patients with higher baseline A1c values

15   had greater mean reductions in A1c. Also, based on

16   dapa's mechanism of action being dependent on renal

17   function, patients with higher baseline eGFR values

18   had greater mean reduction in A1c.

19   Efficacy was reduced but present in those

20   patients with lower estimated eGFR between 30 and

21   less than 60. Subgroup analyses by age suggested

22   that a reduction in A1c lowering may be present in

1   older patients. However, since older age is

2   associated with declining renal function, a

3   preplanned analysis of age, controlling for degree

4   of renal function, was conducted.

5   The results of this test showed that after

6   controlling for changes in estimated GFR, there was

7   no conclusive evidence to suggest that age is an

8   independent factor affecting the efficacy of

9   dapagliflozin.

10   Dapa's target organ is in the kidney, and

11   its mechanism of action is dependent on renal

12   function. In order to better assess safety and

13   efficacy of dapagliflozin in type II diabetes

14   patients with moderate renal impairment, a

15   dedicated study was conducted in patients with

16   eGFR, 30 to less than 60. The primary endpoint was

17   changed in A1c at week 24. Dapa did not lead to a

18   decrease in A1c in this study.

19   These results were somewhat discrepant with

20   the results of the pool subgroup analysis just

21   shown, where there was evidence of modest efficacy

22   in patients with eGFR, 30 to 60.

1   To further investigate this discrepancy, we

2   conducted a post hoc analysis in the two subsets of

3   the dedicated study, those with 3B chronic kidney

4   disease, defined as eGFR 30 to less than 45, and

5   those with 3A chronic kidney disease, with eGFR 45

6   to less than 60.

7   In both subsets, the 95 percent confidence

8   interval for the placebo-corrected A1c difference

9   overlapped zero. However, the point estimates were

10   observed to be different, plus .07 in those with

11   lower mean eGFR, below 45, and minus .33 for those

12   with eGFR, 45 to less than 60, suggesting that the

13   lack of efficacy in this trial was driven by

14   patients with eGFR less than 45.

15   Consistent with this hypothesis, when we

16   evaluated A1c results in patients with eGFR of 45

17   to less than 60 from another source, the nine-study

18   pool, efficacy was similar and the 95 percent

19   confidence interval excluded zero.

20   The totality of data from our pooled

21   analysis, as well as the post hoc analysis in

22   patients with moderate renal impairment,

1   demonstrates that efficacy, while reduced in

2   magnitude, is present in patients with eGFR 45 to

3   less than 60.

4   Efficacy is absent in those with eGFR of

5   less than 45. That corresponds roughly to a

6   creatinine clearance of 60 ml per minute, the

7   sponsor-proposed cutoff for excluding patients in

8   the dapa label.

9   For a drug with the novel mechanism of

10   action being evaluated for chronic disease, it is

11   important to ascertain safety and efficacy over a

12   long-term treatment period. The end-use submission

13   included data of up to two years' duration. A

14   measure of long-term efficacy is the proportion of

15   patients achieving glycemic targets over time.

16   This graph shows the proportion of patients

17   at goal with an A1c of less than 7 percent over 102

18   weeks in the add-on to metformin study. For this

19   endpoint, patients who were rescued, discontinued

20   for any reason, or missing at the time of the

21   visit, are counted as treatment failures.

22   Consequently, no data imputed using LOCF and all

1   patients are included in the analysis at each time

2   point. At week 24, 38 percent of patients treated

3   with dapagliflozin, 10 milligrams, were at goal,

4   corresponding to a 14 percent increase over

5   placebo.

6   At week 1 or 2, 31 percent of patients

7   treated with dapa were at goal, corresponding to a

8   16 percent increase over placebo. Therefore,

9   compared to placebo, proportion of patients to goal

10   were maintained through week 102 at the dapa 10-

11   milligram dose.

12   Results from the extension period of the

13   add-on to-insulin study also support the

14   maintenance of A1c lowering. A1c reduction in the

15   dapa groups versus placebo, observed at week 24,

16   was maintained through the 48-week treatment

17   period. In this study, the mean baseline insulin

18   dose was 77 units per day. Increases in insulin

19   doses were only allowed if patients exhibited poor

20   glycemic control, based on predefined glycemic

21   criteria.

22   Dapa treatment mitigated the need for an

1   increased insulin requirement over time in this

2   study. Illustrated here are the changes to mean

3   daily insulin dose. The flat lines in the graph

4   indicate that mean baseline insulin doses were

5   maintained in dapa-treated patients over a 48-week

6   treatment period, compared to a gradual but steady

7   increase in insulin requirement in the placebo

8   group.

9   Taken together, the data from insulin

10   studies suggest that dapagliflozin treatment helps

11   maintain longer glycemic control while mitigating

12   the need for further insulin requirement in

13   patients with long-standing diabetes, poorly

14   controlled on insulin therapy.

15   Results from our phase 3 program indicate

16   that treatment with dapagliflozin leads to

17   consistent reductions in A1c, fasting plasma

18   glucose, and post-prandial glucose in a broad range

19   of patients with type II diabetes, from drug-naive

20   patients to those with long-standing disease,

21   irrespective of their background therapy.

22   Of the three doses extensively studied in

1 phase 3, the recommended daily dose of

2 10 milligrams was most effective. The 10-milligram

3 dose had numerically greater reductions in glycemic

4 parameters than 5 milligrams. Also, A1c reduction

5 with 10 milligrams is comparable to the commonly

6 prescribed oral anti-diabetic agents such as

7 metformin XR and glipizide.

8   In addition to glycemic efficacy, the

9 glycosuric effect of dapagliflozin leads to weight

10 loss that is primarily fat loss. In patients

11 inadequately controlled on insulin therapy,

12 dapagliflozin treatment leads to better glycemic

13 control while mitigating the need for further

14 insulin requirement.

15   A1c reduction is consistent across different

16 subgroups of patients, but is influenced by two

17 factors, baseline A1c and baseline renal function.

18 The beneficial effects of dapagliflozin are

19 sustained over the duration of the treatment.

20 Thank you.

21   I would now like to invite Dr. Jim List to

22 present the safety of dapagliflozin. Dr. List?

Sponsor Presentation – Jim List

DR. LIST: Thank you, Dr. Parikh.

Good morning. The safety profile of dapa is established through an extensive non-clinical program and a large clinical trial program. The non-clinical program did not identify safety concerns even at high exposure multiples, with no adverse effect levels in chronic toxicity studies of up to 12 months' duration in rats at 300 times the human exposure, in mice at 600 times the human exposure, and in dogs at 3,000 times the human exposure level at the 10-milligram dose. In the clinical program, safety was characterized by pooling data across studies.

There were 14 phase 2b and 3 studies in the dapa NDA file. Green bars represent completed studies. Orange bars represent studies with ongoing long-term phases at the time of filing. The studies in orange have variability in long-term exposure because of their ongoing nature, but all have completed short-term phases. The most complete and best-controlled dataset for safety

1   analysis is composed of the short-term phases of 12

2   placebo-controlled studies, outlined in green.

3   This short-term placebo-controlled pool

4   excludes long-term phases to avoid confounding by

5   dropouts and rescue medications. It excludes the

6   active comparator study versus sulfonylurea to

7   allow for a clean placebo comparison. And it

8   excludes the study on moderate renal impairment,

9   which looks at a different population than the

10   overall phase 3 program, and includes patients for

11   whom dapa is not recommended.

12   To look for safety signals arising from

13   longer exposure, we use a pool composed of data

14   from the five studies in the placebo-controlled

15   pool that had long-term data at the time of filing.

16   Finally, to characterize rare events, the

17   totality of available data from all 14 studies is

18   pooled in an all phase 2b/3 pool. In the dapa NDA

19   column, a total of 4,287 patients were treated at a

20   dose of 2.5 milligrams or higher, with over 2,000

21   treated for one year, 1,300 for 18 months, and over

22   400 for two years. The long-term exposures were

1   even larger at the four-month safety update, with

2   over 900 patients exposed for at least two years.

3   Of the more than 4,000 patients receiving dapa,

4   roughly half received 10 milligrams, the proposed

5   usual clinical dose.

6   Demographic and baseline characteristics

7   were balanced between dapa and control, and are

8   typical for phase 3 clinical trial diabetes

9   populations. The bottom parameter, duration of

10   type II diabetes, varies by study from around two

11   years in the monotherapy studies to well over

12   10 years in the add-onto-insulin setting.

13   The frequency of adverse events was similar

14   between dapa and placebo. In the first row, the

15   percentage of patients having at least one adverse

16   event was 61.5 percent for dapa, 10 milligrams, and

17   56.9 percent for placebo. Serious adverse events

18   were reported for 3.5 percent of patients receiving

19   dapa, 10 milligrams, and 3.3 percent of patients on

20   placebo. Adverse events leading to discontinuation

21   from study medication occurred in 3.2 percent of

22   patients on dapa, 10 milligrams, and 2.5 percent of

1   patients on placebo. Deaths were rare in the

2   program, occurring in 0.5 percent of patients

3   receiving dapagliflozin and also 0.5 percent of

4   patients on control.

5   Safety topics being presented are shown

6   here. First, we will present data on topics of

7   interest because of the mechanism of action,

8   hypoglycemia, urogenital infections, blood pressure

9   changes, renal function, laboratory data, and bone

10   health. After mechanism-related topics, we will

11   present unexpected safety findings related to

12   malignancies and to hepatic safety. Finally, we

13   will present the findings of a cardiovascular meta-

14   analysis.

15   Hypoglycemia is a concern with any glucose-

16   lowering drug. As expected, higher rates of

17   hypoglycemia were observed when dapa was studied in

18   combination with sulfonylurea or with insulin,

19   shown in the plus SU and plus insulin rows at the

20   bottom.

21   In monotherapy, or in combination with

22   metformin, or with pioglitazone, the proportions of

1   subjects experiencing hypoglycemia was low and

2   similar to placebo. Thus, while dapa appears to

3   have a low intrinsic propensity to cause

4   hypoglycemia, it can enhance the hypoglycemic

5   tendencies of other agents.

6   Urinary tract infections and genital

7   infections are common in patients with diabetes,

8   with urinary glucose thought to be a risk factor

9   for these. We have performed broad analyses of

10   adverse events that are suggestive of these

11   infections, as shown in the FDA briefing book.

12   We've also performed more specific analyses of

13   adverse events that are diagnoses of these

14   infections, which are shown in the sponsor briefing

15   book and in the current presentation.

16   In general, the two types of analyses are

17   concordant. Diagnoses of urinary tract infection

18   were more common with dapa than placebo. At the

19   top of this table, UTIs were seen in 4.3 percent of

20   patients on the 10-milligram dose and 3.7 percent

21   of patients on placebo. A similar increase in

22   these infections was seen at the 5-milligram dose.

1   The middle of the table shows the experience

2   in female patients, where, again, the 10-milligram

3   dose had a higher UTI rate of 7.7 percent and

4   placebo at 6.6 percent. At the bottom is the

5   experience in male patients, where the frequency of

6   these infections was lower.

7   These infections were generally graded as

8   mild to moderate and responded to an initial course

9   of therapy without interrupting dapa treatment.

10   There was no increasing in severe urinary tract

11   infections. In the entire clinical program, there

12   were three cases of pyelonephritis on dapa and 4

13   cases on control. Vulvovaginitis and balanitis

14   were also more common in patients treated with dapa

15   than control.

16   The percentage of patients with these

17   diagnoses was 4.8 percent at 10 milligrams versus

18   0.9 percent for control. A similar increase in

19   these infections was seen at the 5-milligram dose.

20   For female patients, the rates were 6.9 percent for

21   10 milligrams versus 1.5 percent for control. And

22   for male patients, it was 2.7 percent for

1   10 milligrams and 0.3 percent for placebo. These

2   infections were also graded, generally, as mild to

3   moderate and usually responded to an initial course

4   of therapy without interrupting dapa treatment.

5   Dapa has a mild diuretic effect, through

6   inhibiting sodium and glucose reabsorption in the

7   proximal tubule. Dapa increases urinary volume at

8   the 10-milligram dose by about 375 milliliters per

9   day or the equivalent of about one extra void per

10   day. Along with this diuretic effect, there tends

11   to be a decrease in blood pressure in patients

12   treated with dapa.

13   In the top graphs, systolic blood pressure

14   decreases by week 1 in the dapa groups and remains,

15   on average, lower than placebo. In the bottom

16   graph, diastolic blood pressure follows a similar

17   pattern. The placebo-subtracted decrease in blood

18   pressure for the 10-milligram dose at week 24 was

19   3.5 millimeters mercury, systolic, and 1.6

20   millimeters mercury, diastolic. Consistent with

21   the modest nature of this blood pressure effect,

22   postural blood pressure measurements, which were

1   taken at every study, showed no increase in

2   orthostatic hypotension with dapagliflozin.

3   Adverse events potentially caused by

4   overdiuresis, that is, events of hypotension,

5   hypovolemia, or dehydration, were uncommon. There

6   were more of these events in the dapa groups than

7   placebo at 0.8 percent on dapa, 10 milligrams,

8   versus 0.4 percent for placebo. These events

9   generally did not result in hospitalization or in

10   discontinuation of dapa therapy.

11   Renal function with dapa therapy was stable.

12   In the overall population as well as in patients

13   with stage 3a chronic kidney disease, in the first

14   week of therapy, there is a clinically

15   insignificant increase in serum creatinine, an

16   increase of 0.03 milligrams per deciliter at the

17   10-milligram dose, representing a small decrease in

18   estimated GFR. This is hypothesized to represent

19   kidney auto-regulatory mechanisms associated with

20   proximal tubular diuresis. Subsequently, there is

21   a gradual return to baseline in serum creatinine,

22   and estimated GFR, and stability for up to two

1   years of follow-up.

2   In the dedicated study in moderate renal

3   impairment, which included both stage 3a and stage

4   3b chronic kidney disease, the pattern was

5   different, with the same initial decrease in

6   estimated GFR being followed by stability without

7   the return to baseline.

8   On an individual patient level, the

9   proportion of patients with outlying values for

10   increases in serum creatinine was similar to

11   control. Renal adverse events, both overall as

12   well as serious adverse events, were also balanced

13   with control. There were no events in patients

14   receiving dapa of acute tubular necrosis or acute

15   nephritis, suggestive of toxic or allergic

16   nephropathy, and no patient experienced end-stage

17   renal disease in the program.

18   Extreme hypoglycemia in the setting of

19   uncontrolled diabetes can overwhelm the kidney's

20   transport capacity and lead to glucosuria,

21   accompanied by significant electrolyte losses. In

22   contrast, the controlled pharmacological glucosuria

from SGLT2 inhibition with dapagliflozin does not

lead to alterations in the major serum electrolytes

sodium, potassium, chloride, or bicarbonate.

Dapa promotes uric acid excretion, leading

to a decrease in serum uric acid. Dapa is also

associated with an increase in hematocrit,

occurring over the first 12 to 16 weeks of therapy,

and then remaining stable with a 2.15 percent

increase over baseline at the 10-milligram dose.

There was no increase in thromboembolic events

associated with this increase in hematocrit.

Bone health was investigated because of the

role of the proximal tubule in regulating calcium

and phosphate homeostasis. With dapa, there was no

effect on urinary calcium or on serum calcium

concentration. Mean magnesium phosphorus and

parathyroid hormone concentrations increased only

slightly, staying well within the normal range; 25

hydroxy vitamin D and 125 dihydroxy vitamin D did

not change with dapa.

Overall, there was no increase in bone

fracture risk with dapa therapy. In the non-

1   clinical program, there were no calcium or bone

2   effects in mice or in dogs. Rats, when exposed to

3   high doses of dapa in toxicology studies, had an

4   increase in trabecular bone thickness and strength.

5   In patients, there was no clinically or

6   statistically significant effect on bone mineral

7   density, measured at the lumbar spine, femoral

8   neck, and total hip after one year of therapy with

9   dapagliflozin. Consistent with the bone density

10   data in the overall clinical program, the

11   percentage of patients experiencing fractures on

12   dapa was similar to control at 1.3 percent for dapa

13   and also 1.3 percent for control.

14   The fracture experience was different,

15   however, in the dedicated study in patients with

16   moderate renal impairment. In this study, there

17   were 12 fractures in the two dapa study arms and no

18   fractures on placebo. Eight of the 12 fractures on

19   dapa in this study were in patients with stage 3b

20   chronic kidney disease. When we pool our placebo-

21   controlled data with patients with moderate renal

22   impairment and stage 3a chronic kidney disease,

1   that is, the patients in whom dapa shows some

2   efficacy, we see a similar proportion of patients

3   with fractures on dapa as on placebo.

4   Because we see no non-clinical sign for bone

5   fragility, no effect of dapa on bone mineral

6   density, and no increase in fractures with dapa in

7   the overall program, or in the patients with

8   moderate renal impairment, in whom dapa is

9   recommended, we conclude that dapa therapy does not

10 pose an increased risk of fracture. However,

11 because of the imbalance in fractures in the

12 dedicated study in moderate renal impairment, we do

13 plan to continue to monitor fracture data post-

14 approval, as Dr. Daniels will describe.

15   With completion of the phase 3 program,

16 safety concerns not related to the mechanism of

17 dapa have emerged. In the dapa clinical program,

18 while overall malignancies are balanced, there have

19 been more bladder and breast cancers in patients

20 taking dapa than control. There is little

21 biological plausibility for dapa playing a

22 causative role in these tumors. In non-clinical

1   testing, dapa has shown no potential to be

2   carcinogenic in humans. Dapa is highly selective

3   for SGLT2 with greater than 1400 full selectivity

4   versus other members of the sodium glucose co-

5   transporter family.

6   Secondary pharmacology screens show no

7   significant off-target interactions with dapa or

8   its major metabolite at over 300 targets, including

9   androgen and estrogen receptors. Predictive

10   computational structure activity models raise no

11   alerts for dapa or its major metabolite, and there

12   are no reactive metabolites of dapa, the major

13   metabolite being a stable ether glucuronide.

14   Dapa is not genotoxic in Ames mutagenicity

15   or in vivo clastogenicity assays. And there's no

16   known linkage between the mechanism of action and

17   tumor risk, with SGLT2 expression being highly

18   selective for the kidney and not detected in human

19   breast or urinary bladder tissue.

20   Finally, in two-year rodent carcinogenicity

21   studies, dapa was not found to be carcinogenic.

22   There were no increases in tumors at exposures

105-fold higher in mice and 186-fold higher in rats

than the human exposure at the 10-milligram dose.

Of note, these models, with the study

designs employed, are able to identify known human

bladder and breast carcinogens. And there are no

agents that we are aware of with this clean of

preclinical profile that were subsequently found to

be carcinogenic in humans.

In addition, there were no hyperplastic

changes seen in breast or bladder tissue in these

animal studies, indicating that dapa is not only

not a carcinogen, but that it is also not acting as

a tumor promoter in these tissues. The overall

clinical data also show no evidence for

carcinogenicity. The overall incidence of tumors

that are either malignant or unspecified regarding

their malignancy was similar over time for dapa in

control.

Our most recent analysis of malignancies

takes into account data through May of this year.

It includes data beyond the filing in the four-

month safety update. As a result of using this

1 later time point, our analysis will reflect

2 additional events beyond those in the FDA briefing

3 book.

4 At the top is shown the overall malignancy

5 incidence rate difference in an analysis stratified

6 by study between dapagliflozin and control. Below

7 that are the incidence rate differences between

8 dapa and control by tumor origin. The bottom three

9 tumor types are gender-specific, with incidence

10 rates for these tumors calculated on a gender-

11 specific exposure basis.

12 Some types of malignancy were seen more

13 commonly on control, such as renal, respiratory

14 tract, or female reproductive cancers. Other types

15 were seen more commonly on dapa. Of these, the

16 largest numerical imbalances were in bladder and

17 breast malignancies.

18 A numerical imbalance was also seen in

19 prostate cancer. However, two of the cases of

20 prostate cancer on dapa were diagnosed within the

21 first week of therapy, and, therefore, cannot be

22 attributed to study drug, and a third case happened

1   within seven weeks. Excluding these cases,

2   prostate cancer is roughly balanced with control.

3   For bladder cancer, there were seven cases

4   on dapa and no cases on control. The 95-percent

5   confidence interval for the incidence rate

6   difference spanned zero; that is, the statistical

7   analysis does not rule out this imbalance being a

8   chance finding, nor does it rule out a role for the

9   drug.

10   Three additional cases of bladder cancer

11   have recently been reported in ongoing clinical

12   trials, two on dapa and one on control. This

13   brings the current total to nine cases on dapa and

14   one case on control. Taking the additional new

15   cases into account, the incidence rate difference

16   remains unchanged and the 95-percent confidence

17   interval continues to span zero.

18   For breast cancer, there were nine cases on

19   dapa and one case on control. Similar to bladder

20   cancer, the statistical analysis of breast cancer

21   neither rules out the imbalance being a chance

22   finding, nor rules out a role for the drug.

The cancer cases in dapa-treated patients had clinical characteristics reflective of cancer in the general population. All the bladder cancer cases were in males and seven of the nine on dapa occurred at or over the age of 60. Seven of the nine on dapa were in current or former smokers. The dose distribution is similar to that of the overall program, where roughly half the patients receive the 10-milligram dose.

Invasiveness grade and TNM classification are shown. Some of these cancers could have existed before entry into the dapa clinical trials. The median time to diagnosis for the cases on dapa was 393 days, a short time frame for human carcinogenesis, with diagnosis happening as early as 43 days after randomization. And all nine cases on dapa were detected within two years of study entry.

In addition, five of the nine patients with bladder cancer on dapa, as well as the patient on placebo, were found to have had microscopic hematuria at baseline, which can be a sign of

1   preexisting bladder cancer. And two more developed

2   hematuria within six months of randomization.

3   Our analysis of baseline characteristics has

4   not revealed an imbalance in risk factors to

5   account for the numerical imbalance in cases.

6   We've also considered the hypothesis that

7   diagnostic bias could arise from the effects of

8   dapa on urine volume and on urinary tract infection

9   risk. Our analysis does not show a compelling link

10   between these effects of dapa and the cases of

11   bladder cancer identified in the program, though we

12   cannot completely exclude the possibility of such a

13   link.

14   The breast cancer cases in dapa-treated

15   patients also had clinical characteristics

16   reflective of cancer in the general population.

17   Seven of the nine cases on dapa were in females at

18   or over the age of 60. The dose distribution is

19   similar to that of the overall program. Tumor

20   type, grade, TNM classification, and estrogen

21   receptor status are shown.

22   Some of these cancers could have existed

1   before entry into the clinical trials. All nine

2   breast cancers on dapa were detected within one

3   year of randomization, a short time frame for human

4   carcinogenesis. And two of the dapa cases were

5   diagnosed within six weeks of starting therapy.

6   Our analysis of baseline characteristics has

7   not revealed an imbalance in risk factors for

8   breast cancer in the program. And though it has

9   been hypothesized by some that weight loss could

10   lead to easier detection of breast cancer, we have

11   not found conclusive evidence for such a diagnostic

12   bias leading to preferential identification of

13   breast cancer in patients receiving dapa.

14   In summary, dapa does not appear to play a

15   causal role in malignancy. Dapa is not a

16   carcinogen. There is no detected off-target

17   pharmacology, no reactive metabolites, no

18   genotoxicity, no target expression in breast or

19   urinary bladder tissue, and no signal of tumors or

20   hyperplasia in gold standard two-year rodent

21   carcinogenicity studies. Although there are

22   imbalances in bladder and breast malignancies, the

1 small numbers involved limit any statistical

2 inference of causality.

3   The cases of bladder and breast cancer have

4 characteristics that are reflective of cancer seen

5 in the general population. They occur in a short

6 time frame for human carcinogenesis, with some of

7 the cancers potentially having been present prior

8 to randomization. Although there is no compelling

9 evidence linking dapa with cancer, nevertheless, we

10 intend to continue to monitor closely the incidence

11 of bladder and breast cancers in patients treated

12 with dapa in ongoing and future clinical and

13 pharmacoepidemiology studies, as you will hear more

14 about from Dr. Daniels.

15   Dapa, with its kidney-specific mechanism of

16 action, does not show liver toxicity in non-

17 clinical testing. There have been no

18 histopathology findings indicative of liver injury

19 in any non-clinical species at up to a 5,000-fold

20 multiple of the human exposure at the 10-milligram

21 dose.

22   In the clinical program, there was no

1   meaningful effect of dapa on liver test values.

2   Shown are the mean values over time for dapa 2.5,

3   5, or 10 milligrams, or placebo with alanine

4   aminotransferase in the top left panel, aspartate

5   aminotransferase in the top right, total bilirubin

6   in the bottom left, and alkaline phosphatase in the

7   bottom right.

8   On an individual patient level, the

9   frequency of elevations of liver tests was balanced

10   between dapa and control. When we look at the

11   experience with up to two years of exposure, the

12   top rows show the frequency of elevations of ALT to

13   3, 5, 10, or 20 times the upper limit of normal.

14   At each of these thresholds, the frequency of dapa

15   elevations is balanced with control.

16   The middle shows approximately balanced

17   bilirubin elevations. The bottom two rows show

18   combined elevations of ALT or AST greater than

19   three times the upper limit of normal, with total

20   bilirubin greater than two times the upper limit of

21   normal, and of ALT or AST greater than three times

22   the upper limit of normal, with total bilirubin

1   greater than 1.5 times the upper limit of normal.

2   For both of these criteria, the percentage

3   of patients on dapa was similar to control.

4   Although we will not be discussing all of the cases

5   in detail today, the eight cases of elevated serum

6   ALT and bilirubin on dapa that are summarized in

7   the FDA briefing book are represented in the last

8   row.

9   An independent committee was established to

10   adjudicate, in a blinded fashion, the likelihood of

11   the relationship of hepatic events to study drug in

12   the program. Of note, there were no cases of

13   severe liver injury leading to death or

14   transplantation.

15   Thirty-five cases on dapa were adjudicated,

16   as were 17 cases on control, and 2 cases in ongoing

17   clinical trials, in which the treatment assignment

18   still blinded. No cases on dapa and two cases on

19   control were adjudicated as being probably related

20   to study drug, meaning a 50 to 74 percent

21   likelihood of a causal relationship. That this

22   high level of relationship to study drug was found

1   for these two patients, both of whom were receiving

2   placebo, highlights the difficulty of accurately

3   assigning causality. A possible relationship or 25

4   to 49 percent likelihood was found for nine cases,

5   or 0.2 percent, for dapa, and five cases, or 0.3

6   percent, for control. The remainder of the cases

7   were adjudicated, the study drug being unlikely or

8   excluded from a causal role.

9   Of the cases adjudicated as possibly related

10   to study drug, all have alternative explanations or

11   exculpatory features. One of the cases on dapa,

12   however, is of concern because the data are not

13   sufficient to distinguish the alternative

14   explanation, autoimmune hepatitis, from drug-

15   induced liver injury. This case is highlighted in

16   both the sponsor and the FDA briefing books.

17   The patient is a 78-year-old Indian male

18   living in the U.K. Past medical history includes

19   type II diabetes, coronary artery disease,

20   hypertension, dyslipidemia, and benign prostatic

21   hyperplasia. He was taking several concomitant

22   medications. Study medication was metformin,

1   2,000 milligrams, and dapa titrated from

2   2.5 milligrams to 5 milligrams.

3   At baseline, the patient had an elevated

4   ALT. On day 127, the ALT began rising above the

5   baseline. On day 192, as the liver test worsened,

6   dapa was discontinued. From day 196 to 200, the

7   patient was noted to have abdominal discomfort and

8   anorexia. ALT peaked at 1,858 units per liter,

9   more than 35 times the upper limit of normal, and

10   total bilirubin peaked at 4.2 milligrams per

11   deciliter.

12   The liver test then began to improve, with

13   ALT stabilizing between 10 and 15 times the upper

14   limit of normal. On days 263 and 264,

15   respectively, liver ultrasound and biopsy were

16   performed. The pathologist's differential

17   diagnosis of the biopsy specimen was viral agents,

18   drugs, or autoimmune hepatitis.

19   On day 349, immunosuppressive therapy was

20   started for presumptive autoimmune hepatitis. On

21   day 382, after 33 days of prednisolone therapy, the

22   patient's next set of liver tests showed

1   improvement. At this point, the prednisolone was

2   tapered and azathioprine was started. On day 621,

3   the patient, who was continuing on azathioprine,

4   was noted to be clinically very well, with liver

5   tests that were back to his baseline.

6   Laboratory data for the patient include

7   negative viral and autoimmune serologies, though

8   hepatitis C was only tested for at baseline.

9   Immunoglobulins were found to be elevated, and the

10 patient was found to be a compound heterozygote for

11 hemochromatosis, though with only mild cirrhosis on

12 his liver biopsy specimen.

13   The day 621 visit was the last visit before

14 the patient withdrew consent. The patient has

15 declined repeated attempts to get more information

16 regarding his testing and course. The information

17 we have shows a picture of a patient with a liver

18 injury that improved upon discontinuation of dapa

19 and returned to baseline with institution of

20 immunosuppressive therapy.

21   There are features compatible with, but not

22 diagnostic of, autoimmune hepatitis, including the

1   patient's pathology, elevated immunoglobulin

2   levels, and response to immunosuppression. These

3   do not specifically differentiate the case from

4   drug-induced liver injury, and there are features

5   that do not favor autoimmune hepatitis, including

6   the patient's age, and gender, and his negative

7   autoimmune serologies.

8   With the information we have, it is not

9   possible to assign a precise likelihood to the case

10   being drug induced. The FDA, in their briefing

11   book, assign a causality as probably related to

12   study drug. The independent blinded adjudication

13   committee adjudicated the case as possibly related

14   to study drug, but even there, each of the

15   adjudicator's assessments was different, with one

16   voting for unlikely, one for possible, and one for

17   a probable causal relationship.

18   Dapa, with its kidney-specific mechanism of

19   action, does not show liver toxicity in non-

20   clinical testing, with no mechanism for potential

21   to cause liver injury identified. The clinical

22   program shows no imbalance in liver test

1   elevations. And in the entire clinical program,

2   there were no cases of severe liver injury leading

3   to death or liver transplantation. There was,

4   however, one case of hepatitis of concern for its

5   potential relationship to dapa, and because of this

6   case, we plan to continue to assess liver safety

7   into the post-marketing environment.

8   Cardiovascular disease is the leading cause

9   of mortality in patients with diabetes, as you

10   heard from Dr. Buse. Accordingly, we performed a

11   cardiovascular meta-analysis to assess the impact

12   of dapagliflozin on cardiovascular risk. The

13   prespecified primary objective was to assess the

14   relative risk ratio for the primary composite

15   endpoint of cardiovascular death, myocardial

16   infarction, stroke, and hospitalization for

17   unstable angina. There was independent blinded

18   adjudication of all cardiovascular events, and the

19   statistical analysis plan was prespecified prior to

20   unblinding the adjudication results.

21   On the left, the hazard ratio for the

22   primary composite endpoint was 0.674, in favor of

1 dapa, with a 98-percent confidence interval, upper

2 bound of 1.178. In the table on the right, there

3 were 48 events in the dapa group and 30 events in

4 the control group contributing to the primary

5 endpoint. The most common event was myocardial

6 infarction. The annualized event rate was

7 1.1 percent for dapa and 1.6 percent for control.

8   Characterization of dapa's safety profile

9 suggests, consistent with its reliance on the

10 amount of glucose filtered in the kidney, dapa has

11 a low intrinsic propensity to cause hypoglycemia.

12 As anticipated, dapa-induced glucosuria leads to

13 slightly more urinary tract infections, and to more

14 vulva vaginitis, and balanitis.

15   The diuretic effect of dapa is associated

16 with a modest decrease in blood pressure. Renal

17 function remains stable over time with dapa

18 therapy. Laboratory evaluation shows no change in

19 serum electrolytes, a decrease in serum uric acid,

20 and an increase in hematocrit, with no increase in

21 thromboembolic events. Assessment of bone health

22 shows clinically insignificant increases in serum

1   phosphorus, magnesium, and parathyroid hormone, and

2   no effect of dapa on bone mineral density or on

3   fracture rate in patients for whom the drug is

4   recommended.

5   With completion of the phase 3 program, we

6   have identified imbalances in bladder and breast

7   malignancies. The weight of evidence does not

8   favor a causal role in these for dapa. Hepatic

9   data shows no non-clinical signal for liver

10   toxicity and no imbalance in patient liver test

11   abnormalities, but one case of hepatitis of concern

12   for its potential relationship to dapa.

13   Finally, a cardiovascular meta-analysis

14   demonstrates that dapa is not associated with an

15   unacceptable increase in cardiovascular risk.

16   Dr. Gavin will now describe the benefit-risk

17   assessment of dapagliflozin.

18   Dr. Gavin?

19   **Sponsor Presentation - James Gavin**

20   DR. GAVIN: Thank you, Dr. List.

21   Good morning, Chairman Thomas, members of

22   this committee, FDA official, ladies and gentlemen.

1   I'm Jim Gavin, CEO and chief medical officer of

2   Healing our Village, and clinical professor of

3   medicine at Emory and Indiana University Schools of

4   Medicine.

5   I am pleased to have the opportunity to

6   speak to you during these proceedings and provide

7   my views on the matter of the overall benefit-risk

8   characteristics of dapa and the implications for

9   patient care.

10   As a matter of disclosure, I have served as

11   a paid consultant for the sponsor for work on

12   diabetes-related therapies in the past and as a

13   member of its speakers bureau. I hold no stock or

14   other interests. I am a past president of the

15   American Diabetes Association and past national

16   chair of the National Diabetes Education program.

17   I begin by reiterating that diabetes is

18   truly the epidemic of our time. It is a disease

19   colossus among us, whose scope and impact are

20   continuing to outpace our ability to control it.

21   We see the evidence in the mounting prevalence

22   statistics and the growing burdens of

1   complications.

2   While certainly not the only important

3   metabolic contributor to the damaging effects of

4   diabetes, high glucose is a core problem. High

5   glucose is, indeed, how we make the diagnosis, and

6   following glucose levels is largely how we assess

7   our success at controlling this disease.

8   It has become clear that relatively mild

9   increases in glucose levels over time can

10   contribute to a variety of harmful effects to

11   vascular and other tissues. It is equally clear

12   that achievement and maintenance of normal or near-

13   normal glucose levels is one of the more difficult

14   aspects of diabetes management.

15   In fact, in major studies targeting multiple

16   risk-factor reduction in diabetes, reaching and

17   maintaining glucose targets has proven especially

18   problematic for clinicians and patients. This is

19   due, in my view, to multiple reasons, not the least

20   of which is the need for additional pharmacologic

21   tools capable of specifically addressing the core

22   problem of high blood glucose over the entire

1   natural history of the course of diabetes.

2   This becomes especially important as we

3   realize limitations of existing therapies and see

4   possible contraction of our treatment options, as

5   the need for combination approaches to treatment

6   become more apparent.

7   Thus, it is significant that dapa

8   specifically targets the high blood glucose of

9   diabetes and provides clinically meaningful

10   reductions in A1c, fasting, and post-prandial

11   glucose. These effects are produced independent of

12   the beta cell function and are consistent across

13   disease duration over the natural history of the

14   disease, dependent on adequacy of renal function

15   with reduced efficacy in moderate renal impairment.

16   By having a well-defined target for its

17   beneficial treatment effects, this agent provides

18   an opportunity for clinicians to have a relatively

19   straightforward conversation with patients

20   regarding the mechanism by which glucose lowering

21   is achieved. Patients would certainly welcome such

22   a conversation. The urgency to reduce glucose

1   levels in diabetes is matched by the need to

2   achieve this goal without further weight gain, so

3   the reduction in body weight observed with dapa

4   makes it a beneficial additional tool to our

5   treatment arsenal. Dapa-treated patients in the

6   phase 3 studies lost weight and were, indeed, one

7   belt notch smaller in their waist circumference, a

8   meaningful clinical benefit.

9   Given the increased importance of

10   cardiovascular risk reduction in diabetes, it is

11   clinically meaningful that a reduction in blood

12   pressure is seen with dapa use, perhaps

13   contributing to the robust 33 percent reduction in

14   composite cardiovascular endpoints, early

15   observations that warrant additional investigation

16   and clinical confirmation of this promising

17   benefit.

18   The core mechanism accounting for glucose

19   lowering with this drug provides some insights into

20   features of its safety profile. It has low

21   propensity to cause hypoglycemia. There is an

22   increase in urinary tract and specific genital

1 infections that appear responsive to the identical

2 courses of treatment used when these same

3 infections appear in the placebo group and

4 discontinuation of drug treatment was not required.

5 There was no increase in pyelonephritis. The

6 diuresis encountered was mild and did not result in

7 clinically significant effects on fluid, or

8 electrolyte balance, or renal function.

9   Now, in the new paradigm for type II

10 diabetes drug development, patient safety is well

11 served by the large phase 3 programs to

12 characterize efficacy and safety. There is no

13 signal to date of unacceptable cardiovascular risk.

14 The large trial size allows for rare events to be

15 detected, albeit without power for a full

16 assessment of any causal inferences. Thus, it is

17 important that vigilant, detailed post-marketing

18 assessments will be vigorously pursued.

19   These are important steps to assure clarity

20 regarding the particulars of potential clinical

21 risk in the face of what appears, in my view, to be

22 significant potential clinical benefit to patient

1   outcomes. For in dapa, we note an agent that

2   directly addresses the high glucose problem that

3   can be expected to contribute to reduced

4   retinopathy, neuropathy, and nephropathy, its

5   additional effects on reducing weight and blood

6   pressure may contribute to decreases in

7   cardiovascular events. The risk of hypoglycemia is

8   likely to be substantially reduced. A very broad

9   spectrum of patients can be targeted for treatment,

10 irrespective of remaining beta cell function or

11 degree of insulin resistance.

12   Such benefits are clinically highly

13 impactful in light of the burden posed by diabetes

14 but do not obviate the observed increase in

15 specific genital infections and urinary tract

16 infections, which are responsive to available

17 treatments, or the potential increased incidence

18 rate for breast and bladder neoplasms, findings

19 that must be further evaluated, similar to the

20 potential drug-induced hepatic events or the

21 potential increase in fractures in patients with

22 moderate renal impairment, which is an avoidable

1   potential complication by the application of

2   current standards of care.

3   I would posit that after all considerations

4   are weighed, we have a beneficial additional tool

5   being proposed that will help improve patient

6   outcomes. I will now yield the podium to Dr. Brian

7   Daniels to discuss the dapa label and post-approval

8   programs.

9   Dr. Daniels?

10   **Sponsor Presentation – Brian Daniels**

11   DR. DANIELS: Thank you, Dr. Gavin.

12   Good morning. I'm Brian Daniels, and I lead

13   Bristol-Myers Squibb development and medical

14   affairs organizations. Both Bristol-Myers Squibb

15   and AstraZeneca are committed to ensuring the safe

16   and appropriate use of dapa in patients with

17   type II diabetes. At this point in time in

18   development, we have established an advanced state

19   of knowledge of its clinical profile. Our

20   development program is, by our estimation, the

21   largest investigational diabetes medicine program

22   submitted for review, based on the number of

1   patients studied, their duration of exposure, and

2   the continuum of diabetes investigated.

3   Now, as expected, some uncertainties remain

4   about the profile of dapagliflozin. And this is

5   the paradigm for the development of innovative

6   medicines in diabetes. The end of phase 3 is just

7   one point in time in almost a 15-year journey of

8   benefit-risk assessment. For this reason, both the

9   industry and the agency have been focusing on

10   developing new pharmacovigilance and observational

11   tools to innovate and to continue to divine the

12   benefit-risk assessment post-approval to further

13   our understanding.

14   Dr. Gavin is a diabetologist who provided

15   his interpretation on the benefits and risks of

16   dapa for patients. As sponsors, we have attempted

17   to crystalize these points. The identified and

18   expected benefits of dapagliflozin are in the first

19   row, and the identified and precautionary risks in

20   the second. For identified benefits and risks, we

21   have provided estimates of the number needed to

22   treat or harm with dapagliflozin, compared to

control, based on our clinical trial experience.

As you see, many patients treated with dapa experienced improvement in glycemic control without an intrinsic concern for hypoglycemia. One additional dapagliflozin patient reached the hemoglobin A1c target of less than 7 percent for every 7 treated, compared to control. And 1 in 8 patients treated with dapa experienced a 5 percent decrease in their body weight compared to control, and many will experience a reduction in their blood pressure.

The potential benefits are viewed by the sponsor as both scientifically plausible and expected, based on both epidemiological data and trials such as UKPDS. There is a potential for fewer microvascular complications like retinopathy, neuropathy, and renal failure because of the established causal link between improved glycemic control and prevention of these complications.

There is a potential reduction in MACE events, predicated both on the CV meta-analysis that you've just seen, as well as the identified

1   effects on improvements in glycemic control, weight

2   loss, and blood pressure. The definitive

3   demonstration, though, of these potential benefits

4   require large outcome trials, which the sponsor has

5   committed to perform.

6   The identified risks for dapa occur at a

7   lower incidence compared to identified benefits.

8   Thus, one additional genital tract infection will

9   occur for every 25 dapa-treated patients compared

10   to control. And for urinary tract infections and

11   volume depletion, these numbers are 1 in 125 and 1

12   every 400 dapa-treated patients, respectively.

13   The precautionary risks are considered

14   unlikely, based on the preclinical and clinical

15   investigations of dapa. These precautionary risks

16   are fracture in patients with moderate renal

17   impairment, breast and bladder cancer, and hepatic

18   injury.

19   These are the uncertainties that remain in

20   the clinical profile after our phase 3, and we

21   believe our pharmacovigilance,

22   pharmacoepidemiological, and randomized clinical

1   trial will continue to assess their incidence, with

2   the expectation of the discharge of these risks.

3   The safe and appropriate use of

4   dapagliflozin, of course, begins with the product

5   labeling of the known risks. Key elements of the

6   proposed product label are intended to both

7   minimize their occurrence and the impact identified

8   in the dapagliflozin program. And we recommended

9   the following measures in labeling.

10   Exclude patients with an estimated GFR of

11   less than 45, and to assess renal function at

12   initiation of dapagliflozin, and periodically.

13   This cutoff is based on our clinical interpretation

14   of the data. This exclusion, based on renal

15   function, is similar to one that is used for

16   metformin to avoid lactic acidosis. BMS is

17   experienced on the effective education of this

18   exclusion, from its introduction of Glucophage to

19   the United States in the 1990s.

20   Minimize the risk in patients' susceptible

21   volume depletion, such as patients on loop

22   diuretics, by using the 5-milligram dose, an

1   interruption of dapagliflozin dosing in patients

2   who develop volume depletion.

3   To reduce the potential for hypoglycemia

4   when dapagliflozin is used in combination with

5   insulin or insulin secretagogues, you should

6   consider reduction in the dose of insulin or those

7   insulin secretagogues.

8   To minimize the impact on patients with

9   pyelonephritis or urosepsis, you should consider

10   interrupting dosing during the periods of acute

11   infections.

12   A complementary set of pharmacovigilance

13   observational studies and large endpoint-driven

14   clinical studies will be used to continuously

15   update the benefit-risk profile of dapa in the

16   marketed space. A surveillance strategy, based on

17   the evaluation of these complementary data sources,

18   addresses the potential limitations associated with

19   any individual one and enables a comprehensive

20   assessment of the post-approval data.

21   For example, spontaneous reports are

22   typically most useful for very rare events.

Pharmacoepidemiological studies are complementary

to both spontaneous reports and clinical trials, by

enabling assessment of uncommon to very rare events

with long latencies in the real-world population.

Large randomized studies provide long-term

controlled experience, too, that avoids the

confounding by indication and enables evaluation of

very small relative risks in conjunction with

periodic monitoring by the data monitoring

committee.

Post-marketing pharmacovigilance practice

will include the evaluation of spontaneous reports

and review of data from ongoing clinical trials.

And these assessments of aggregated safety data

will occur on a monthly basis. In addition,

targeted questionnaires for serious urinary tract

infections, hepatic and renal events, and cancer

reports will be collected, a collection of detailed

data, to understand the timing, nature, risk

factors, and comorbidities for each patient. A

blinded adjudication committee will provide expert

review of both the cardiovascular and hepatic

events reported through our ongoing clinical

trials.

Second, a large pharmacoepidemiological

program will use observational data to compare

patients who are new users to dapagliflozin versus

new users of other anti-diabetic agents in the

real-world clinical setting. These studies will

use existing healthcare databases that include

patients both from the United States and from

Europe, and the studies aim to leverage the

experience of a very large number of patients to

provide estimates of the incidence and risks.

Our pharmacoepidemiological program is

currently designed to study events of severe

complications of urinary tract infections, hepatic

and renal injury, bone fractures, and cancer. The

program will provide for a continued assessment of

the safety profile of dapagliflozin in actual

clinical practice with reports starting

approximately one year after the availability of

dapagliflozin. These observational studies, which

will run for at least five years, will enable a

1   detection of a twofold increase in bladder cancer

2   within two to three years of the approval, based on

3   current estimations.

4   In addition, we plan a large randomized

5   controlled clinical outcomes study. It will enroll

6   patients with type II diabetes with the potential

7   follow-up from a median of four years. The trial's

8   primary hypothesis is a benefit in cardiovascular

9   MACE events in patients using dapagliflozin, with

10   respective adjudication events and prespecified

11   analyses. This hypothesis is supported, again, by

12   the CV meta-analysis of the current program as well

13   as the identified benefits on glycemic control,

14   weight loss, and blood pressure.

15   Additionally, this study provides a means

16   for a continued assessment of the safety profile of

17   dapagliflozin post-approval in a controlled trial

18   setting with long-term treatment and follow-up.

19   The sample size will reflect the objective of

20   providing both meaningful additional information

21   about the events of fracture, cancer, and liver

22   injury, as well as providing definitive information

1   about CV benefit. Thus, we commit to a series of

2   complementary activities for assessment of the

3   benefits and risks of dapagliflozin in the

4   immediate time frame with pharmacovigilance, in the

5   intermediate time frame with observational studies,

6   and long term with the clinical outcomes study.

7   In the cardiovascular and metabolic disease

8   area, both Bristol-Myers Squibb and AstraZeneca

9   have established a history of characterizing the

10   long-term benefits of agents such as pravastatin,

11   rosuvastatin, and clopidogrel.

12   Specifically for saxagliptin, our DPP-4

13   inhibitor, we have already enrolled over 10,000

14   patients of an expected 16,000 patients in the

15   SAVOR cardiovascular outcomes study, working with

16   the TIMI group in less than 30 months from

17   commercialization of saxagliptin.

18   We plan to continue this legacy with

19   dapagliflozin. We are excited about the

20   opportunities of its contribution to the

21   improvement and care of patients with type II

22   diabetes. Thank you and we look forward to

1   discussion.

2   Elizabeth?

3   **Clarifying Questions from the Committee**

4   DR. THOMAS: I'd like to thank the sponsor

5   for their presentations. We'll now take clarifying

6   questions from the committee. Please raise your

7   hand, and we'll recognize you. And while people

8   are raising their hands to ask questions, if we

9   could have Dr. McBryde just introduce himself for

10   the record.

11   DR. MCBRYDE: Good morning. My name is

12   Kevin McBryde. I'm a pediatric nephrologist and

13   currently project officer and program director at

14   the National Institute of Diabetes, Digestive and

15   Kidney Diseases.

16   DR. THOMAS: Dr. Veltri?

17   DR. VELTRI: Thank you, just a couple of

18   quick questions. You've characterized a lot of the

19   effects of the drug on hemodynamics. I was

20   specifically interested in knowing whether or

21   not -- regarding macrovascular risk, cardiovascular

22   risk, is there any data on lipids or

1   proinflammatory markers, obviously, in these

2   patients at risk for cardiovascular events,

3   specifically LDL, or lipoprotein analyses, or

4   hs-CRP, interleukin-6?

5   The second question is, in regards to

6   slide 54, where there seemed to be an impressive

7   early reduction in blood pressure, like at one

8   week, was there corresponding changes in heart rate

9   in those patients? You mentioned the thorough QT

10   syndrome. There wasn't any change in QT nor heart

11   rate, so just a clarifying question there.

12   DR. SVANBERG: Dr. List will address the

13   question. Dr. List?

14   DR. LIST: So to take your questions in

15   order, first, the proinflammatory markers, second,

16   the effects on lipids, and the third is effects on

17   heart rate.

18   Starting with proinflammatory markers, we

19   did look at hs-CRP, fibrinogen, and PI-1 (ph) in

20   two phase 3 studies. We have not looked at IL6.

21   There are no meaningful changes in any of these

22   markers. There's a little bit of downward trend

1   for hs-CRP, but we also see that in placebo. So it

2   doesn't look different from that.

3   With respect to lipids, if I may have slide

4   46-1, please, we see lipid changes as illustrated

5   here, with small increases in HDL and LDL

6   cholesterol. And when we look at the LDL to HDL

7   ratio, it goes down in all study groups, including

8   placebo.

9   With respect to heart rate, we did not see a

10   heart rate change with the changes that we saw in

11   blood pressure. So across the program, there was

12   no change in heart rate from baseline.

13   DR. THOMAS: Dr. Seely?

14   DR. SEELY: I had several GU-related

15   questions. First of all, you showed data on the

16   serum potassium. As we know, serum potassium is

17   not necessarily a good reflection of total body

18   potassium. So I wanted to know if you had done

19   24-hour urine determinations of potassium to

20   compare drug versus their interventions and whether

21   you had looked at 24-hour urine magnesium.

22   The other question I had was what formula

1   did you use for your eFGR [sic] in your studies?

2   Then my last question was, did you see, in

3   terms of the individuals getting the GU infections,

4   were they recurrent, ever, in the same individual?

5   Was there a time course that it was more likely at

6   a certain point in initiation of therapy than in

7   another point of therapy?

8   DR. SVANBERG: I will ask Dr. List to

9   address the question about electrolytes, as well as

10   the pattern of urinary tract infections. And as

11   Dr. List makes his way up here, I clarify that we

12   used the MDRD equation for estimated glomerular

13   filtration rate.

14   Dr. List?

15   DR. LIST: We measured urine electrolyte

16   excretions in 24-hour urines in the phase 2b

17   dose-ranging studies. So this was a study that

18   looked between 2.5 and 50 milligrams of

19   dapagliflozin and had about 50 patients per study

20   group. We did not see any change from baseline in

21   24-hour urinary potassium or magnesium in this

22   study.

1   With respect to the recurrence and timing of

2   genital urinary tract infections, there are two

3   things to note. One is, in our program, we allowed

4   patients in who had a history of recurrent genital

5   infections. These people had a higher rate of

6   genital infections, both on placebo as well as on

7   dapagliflozin. Overall, there was a higher rate of

8   genital infections on dapagliflozin and there were

9   more recurrences of genital infections, as you

10   would expect when you have this differential.

11   The timing, if I may have the Kaplan-Meier

12   plot for the genital infections, of the genital

13   infections, shown on slide 33-1, is such that most

14   of the infections that we saw in the program -- and

15   this is true for the urinary tract infections as

16   well -- were appreciated in the first six months of

17   therapy and then things start leveling off a little

18   bit.

19   DR. THOMAS: Dr. Brittain?

20   DR. SEELY: Can you tell what formula was

21   used for eFGR [sic] formula?

22   DR. SVANBERG: The eGFR formula was --

1   DR. SEELY: What formula was used for

2   eFGR [sic]?

3   DR. SVANBERG: The MDRD formula.

4   DR. SEELY: Thank you.

5   DR. BRITTAIN: Yes. I have two questions.

6   The first one is, what was the exact basis for

7   determining 45 as your cutoff for the GFR? I mean,

8   was it just that you saw that the results would

9   look better in the 45 to 60 versus the 30 to 45

10   subgroups, or was there more analysis involved in

11   that?

12   DR. SVANBERG: I will ask Dr. Parikh to

13   address the evaluation we did for the renal cutoff.

14   Dr. Parikh?

15   DR. PARIKH: So as we enrolled patients in

16   our phase 3 trials, we did not have an eGFR cutoff.

17   We used the metformin criteria to have the

18   patients. And about 87 percent of our patients had

19   an eGFR of more than 60, and we had 12 to

20   13 percent with an eGFR below 60. And most of

21   these patients were in the 45 to 60 category. They

22   were closer to 60 rather than closer to 30.

1   We saw, as we did the subgroup analysis,

2 that there is an effect of renal function and the

3 efficacy is lesser than what we saw that these

4 patients had, A1c reductions in the .35 percent

5 range.

6   We then looked at urine glucose excretions

7 in these patients, particularly in the moderate

8 renal impairment study, the subgroup 45 to 60. The

9 glucose excretion is 30 grams per gram of

10 creatinine per day, which is about 60 percent of

11 the glucose excretion that we see in other trials.

12   We looked at fasting plasma glucose

13 reductions. They were there, 25 milligrams per

14 deciliter compared to placebo. And there was a

15 weight change of 2 kilograms versus placebo. This

16 was done to make sure that there are effects on

17 these patients.

18   Regarding the cutoff, it was very clear from

19 our subgroup analysis that efficacy is reduced, but

20 we do have efficacy. When we did our moderate

21 renal impairment study, we actually enrolled

22 patients who were well divided between the 30 to 45

1   and 45 to 60 cutoff, and we saw these patients

2   behave differently with respect to these

3   parameters, including urine glucose estimation.

4   The cutoff of 45 separates 3a and 3b chronic

5   kidney disease. And when the MDRD equation is

6   applied to Cockcroft-Gault, it roughly equals under

7   60 ml per minute, which is what is for metformin

8   label when we were recruiting the studies and which

9   are the patients we got in our trials where there

10   was this modest efficacy.

11   DR. BRITTAIN: I had a second question.

12   Yes. My second question is more kind of a

13   technical question about a lot of the safety

14   analyses pool across studies. But except for the

15   cardiovascular studies, I don't believe they

16   stratify by study.

17   Is that correct?

18   DR. SVANBERG: Dr. List?

19   DR. LIST: Generally, that is correct. We

20   did not stratify by study for the majority of our

21   safety analyses. Where we did stratify by study

22   was for the cardiovascular analysis and for the

1   cancer analyses, the cancer by tumor type with the

2   incidence rate differences.

3   DR. THOMAS: Dr. Piantadosi?

4   DR. PIANTADOSI: Yes. With regard to the

5   malignancy rates, inside 65, you showed us the

6   incident rate differences.

7   Do you have a similar slide for rate ratios?

8   DR. SVANBERG: We have a slide for that, and

9   also we have a comparison on what the two different

10   methodologies would show. I'll ask Professor Wei

11   to address that question.

12   Professor Wei, please?

13   DR. WEI: L.J. Wei, professor of

14   biostatistics from Harvard. I'm a paid consultant

15   to the meeting. So the question is, we have the

16   results presented using risk of differences.

17   Dr. Piantadosi wants to know the corresponding

18   meta-analysis results using, for example, risk

19   ratio or incidence ratio.

20   So if I may have this slide up, please?

21   So this is a very interesting slide. To

22   illustrate the methodology, if you notice, on the

1   left-hand side, we have 19 studies, and this is

2   risk of difference. Every study, we can construct

3   95 percent confidence interval, even if there is no

4   event. For example, zero minus zero is still zero.

5   But as you know, Steve, we cannot have a

6   variance, but we can get the exact confidence

7   interval. But on the right-hand side, we use a

8   risk ratio or a coincidence ratio. You notice

9   about 10 studies, we couldn't even use it because

10   zero divided zero, we don't know how to define it.

11   So you can see the difference between the two

12   analyses.

13   So on the left-hand side, the meta-analysis

14   confidence interval is very tight, but if you use a

15   risk ratio, because you sacrifice 10 studies, the

16   confidence interval is still so big. So that's the

17   problem. For rare events, we don't like to use a

18   risk ratio.

19   DR. PIANTADOSI: Thank you.

20   DR. THOMAS: Dr. Gregg?

21   DR. GREGG: Yes. I had a question about the

22   efficacy. You showed some data indicating that

1   efficacy may decline with age, and you commented

2   that this may be explained by the chronic kidney

3   disease. But it wasn't really clear, to me, to

4   what extent that was the case, and is this a

5   separate group or is the declining efficacy with

6   age simply explained by renal function?

7   DR. SVANBERG: I'll ask Dr. Parikh to

8   address the question. Dr. Parikh?

9   DR. PARIKH: Yes. So once we had the

10   subgroup analysis done, and it showed that age

11   could be one of the factors that could affect the

12   efficacy of dapagliflozin, and we had anticipated

13   the relationship between age and renal function, we

14   had an analysis that was pre-planned that we did,

15   where we had each of the eGFR categories divided

16   into age below and above 65.

17   Can I have slide 25-15, please?

18   So this is an analysis which includes the

19   nine-study pool that is used for interaction

20   testing. It was the next step in our understanding

21   of any association with age. On the left side are

22   the three categories of eGFR. In each of these

1   categories, we have patients below and above

2   65 years.

3   We looked for a focus interaction test to

4   see if there were any differences between the two

5   age groups; was it because of random variability or

6   was there a systematic reason for that, after

7   explaining for eGFR. So in the right top-hand

8   corner, there is the subgroup interaction value,

9   which was .29. Our limit was .1 for any

10   significant interactions.

11   What we are saying is that we don't have

12   conclusive evidence to suggest that age, by itself,

13   is affecting efficacy if renal function is taken

14   into account. We also did exposure response

15   modeling that suggested and confirmed the findings

16   of subgroup analysis, that once gender, and renal

17   function, and these factors are taken into account,

18   age, by itself, was not an independent factor that

19   would affect the efficacy of dapagliflozin.

20   DR. THOMAS: Dr. Spruill?

21   DR. SPRUILL: I have a question about the

22   subgroups, particularly slide 35. I guess I need

1   some clarification on region. And is it correct to

2   say that this is a multi-country clinical trial?

3   And if so, what percentage came from U.S.?

4   DR. SVANBERG: The dapagliflozin program was

5   a global program and approximately 30 percent from

6   the program came from North America. Twenty-seven

7   percent came from the United States.

8   DR. SPRUILL: So out of this 27 percent from

9   the U.S., what percentage of that was

10   underrepresented minorities?

11   DR. SVANBERG: The African-American

12   population was 3 and a half percent of the overall

13   patient population. That corresponds to

14   9.5 percent of the patients recruited in the U.S.

15   The Asian patient population was around 3 percent

16   from the U.S. population. But the program was also

17   conducted in Asian countries, giving a total

18   proportion of about 10 percent in the program as a

19   whole.

20   DR. SPRUILL: So is it safe to say you're

21   comfortable saying, then, that the efficacy and the

22   safety of dapa in underrepresented minorities is

1 good, based on what the percentages are,

2 understanding that underrepresented minorities have

3 a higher burden of diabetes and complications?

4 DR. SVANBERG: Based on the development

5 program, the proportion of African-Americans or

6 Asians represent the demographic of the United

7 States population, approximately. I totally agree

8 with you that there is a higher proportion of

9 minorities having diabetes than in the overall

10 population, than the known minority population, but

11 the proportion is representative of the U.S.

12 population.

13 Aware of the limitation of the

14 interpretation of the data, we also looked into our

15 phase 1 program, where we evaluated

16 pharmacokinetic, pharmacodynamic effects of

17 dapagliflozin, and there we had between 40 and 50

18 percent being African-Americans. In that respect,

19 there was no difference between the Caucasian and

20 the African-American population.

21 DR. THOMAS: Last question for this session,

22 Dr. Strader?

1   DR. STRADER: I have a couple of questions

2   about the hepatotoxicity and how that was

3   evaluated. It appears that you did some baseline

4   testing for liver-associated enzymes. Did you do

5   any testing prior, say about six months prior, to

6   get a pattern of what the patients' liver enzymes

7   were?

8   It appears, also, that you permitted the

9   inclusion of patients who had abnormal liver

10   enzymes at baseline. Was there any evaluation of

11   what may be the diagnosis of those abnormal liver

12   enzymes? Were there CT scans, or ultrasounds, or

13   something done to try to figure out why there was a

14   baseline abnormality?

15   Thirdly, there were patients on herbal

16   medications. Was there any evaluation of what

17   those herbals were and their potential risk for

18   hepatotoxicity? And what was the exact protocol

19   once you found an abnormality? How often were

20   patients' liver enzymes evaluated? What was the

21   time point at which imaging studies were done? Was

22   there a hepatology consult, those kinds of issues?

1   DR. SVANBERG: So if I understood your

2   question correctly, you asked if we evaluated

3   patients who had liver enzymes higher than 3 who

4   were excluded at baseline. You asked whether we

5   evaluated herbal impact on liver evaluations and

6   how the evaluation was taking place.

7   I do think I missed your very first

8   question, if you could be so kind and repeat that.

9   DR. STRADER: Did you look at patients'

10   liver enzymes about six months prior to coming into

11   the study to see what the pattern was before they

12   were admitted into the study?

13   DR. SVANBERG: So I will ask Dr. List to

14   address these questions. As Dr. List makes his way

15   up here, I can say we did not evaluate liver

16   enzymes at six months prior to coming into the

17   study. That was not done. We did not evaluate

18   patients as regards to what was the reason for

19   their ALT above the exclusion rate, either. And

20   Dr. List will address the herbal medications, as

21   well as the ongoing evaluation across the program.

22   Dr. List?

1   DR. LIST: We started our evaluation of

2   liver tests when patients came into the trial at

3   screening and don't have prior history. With

4   respect to the data that we do collect on the

5   patients, we collect all concomitant medications,

6   including herbal medications on the patients.

7   We haven't done a broad look at patients on

8   herbal medications as a subgroup, but what we do is

9   we look into the cases of interest because of

10   either hepatic events or elevations of liver tests,

11   at their medications and possible confounding

12   factors.

13   In addition, as the program went on, we saw

14   the index case, the case that I described, in 2009.

15   And about that time, the FDA liver guidance came

16   out as well. And so what we did at that point is

17   amend our protocols across the board. And it took

18   from July through December of 2009 to get these

19   amendments into place. And in these amendments,

20   what we've done is we've established mechanisms and

21   an algorithm for following liver test

22   abnormalities. And the algorithm includes repeat

1   testing, getting a battery of other tests, specific

2   questions about possible confounding factors,

3   including herbal medications, and, ultimately,

4   depending on the direction of the case through the

5   algorithm, consultation with a hepatologist.

6   DR. THOMAS: For those members of the panel

7   who are unable to have their question asked, we

8   have time later today. We'll get to those

9   questions at that time. We're now going to take a

10   break, and we will return at 10:30.

11   Panel members, please remember there should

12   be no discussion of the meeting topic during the

13   break amongst yourselves or of any member of the

14   audience. Thank you.

15   (Whereupon, a recess was taken.)

16   DR. THOMAS: We will now proceed with our

17   presentation from the FDA. I would like to remind

18   public observers at this meeting that while this

19   meeting is open for public observation, public

20   attendees may not participate except at the

21   specific request of the panel.

22   Dr. Norton?

FDA Presentation - Jonathan Norton

DR. NORTON: Hello. My name is Jonathan
Norton. I'm with the Office of Biostatistics at
the Center for Drug Evaluation and Research at FDA.
Today, I'll be talking about the evidence for
efficacy for dapagliflozin, or I'll also call it
dapa.

The applicant submitted 11 phase 3 studies
for this NDA and in consultation with the medical
team, I decided to put my most intense focus on six
of the studies, which are shown in the next slide.
These studies were chosen to span a typical
development plan for type II diabetes. For these
studies, I reproduced the applicant's calculations
myself and conducted additional analyses, including
a sensitivity analysis, which I will show you. In
order to put the results of these six studies in
context, I will also discuss some results that the
applicant reported for the other five studies.

So these are the six studies that I closely
reviewed. The first study was a monotherapy study
in drug-naive subjects. The next three were add-on

1   studies in patients whose illness had not been

2   adequately controlled by their current therapy,

3   either metformin, pioglitazone, or insulin. The

4   fifth study used glipizide as an active control,

5   and both dapa and glipizide were added to

6   metformin. Finally, the sixth study tested a

7   combination of dapagliflozin and metformin in drug-

8   naive subjects with a hemoglobin A1c of 7.5 percent

9   or higher.

10   Although the studies varied in design, in

11   the interests of time, I will just summarize the

12   key features. They were all parallel-arm designs.

13   In all of these six studies, the primary endpoint

14   was changed from baseline HbA1c. All but the

15   glipizide-controlled study, which I call study C4,

16   used a test for superiority at week 24. Study C4

17   tested for non-inferiority at week 52, and all but

18   study C4 included glycemic rescue therapy.

19   The primary efficacy analysis was an

20   analysis of covariance, or ANCOVA, with adjustment

21   for baseline hemoglobin A1c, as well as study-

22   specific factors. Missing data were imputed using

1   last observation carried forward, or LOCF

2   imputation. If a subject received rescue

3   medication, then the subsequent observations were

4   excluded from the analysis. Rather, the pre-rescue

5   value was carried forward. Although FDA has

6   essentially recommended LOCF for diabetes studies

7   in the past, this method is now less favored. I

8   will discuss this point after I review the results

9   for the primary endpoint.

10   This table shows the results for the four

11   placebo-controlled studies out of the six. Note

12   that, although I say placebo controlled, all but

13   study 2013 included background therapy. For study

14   2013, there are arms with both A.M. and P.M.

15   dosing. The primary results, which I show, were

16   based on A.M. dosing. The black rows show the

17   least squares' adjusted mean change from baseline

18   for each dose. The blue rows show the various

19   doses of dapa compared to placebo.

20   A negative value indicates that dapa -- so a

21   negative value in one of these rows indicates that

22   dapa had a greater reduction in HbA1c than placebo.

1   Also, I have N here as the size of the primary

2   analysis set in each study.

3   While I did not include the N, the sample

4   size, for each arm, they were roughly balanced.

5   For example, in 2013, there were four arms with

6   roughly an equal number of patients. Note,

7   however, that more patients received dapa overall

8   than placebo because there were multiple dapa arms

9   in each study.

10   As the table shows, every dapagliflozin arm

11   beat the comparator in each study. Despite the

12   varied background therapies, the estimated effect

13   of dapa versus the comparator is fairly consistent.

14   In the 10-milligram arms, the difference ranged

15   from .54 percent to .66 percent. So these are the

16   10-milligram arm results.

17   Note that when I say a difference of .54

18   percent, I am speaking of an absolute difference in

19   HbA1c, which is itself a percentage. In the

20   5-milligram arm, the effect ranged from .40 percent

21   to .54 percent. The effect -- I mean, that was a

22   negative value, less than placebo. Note, however,

1   that these estimates are based on LOCF imputation.

2   As I will discuss later, these may be optimistic

3   estimates of the actual treatment effects.

4   However, I concur with the applicant that there is

5   a real non-zero treatment effect.

6   This slide shows the results for the initial

7   combination study with metformin. So you can see

8   here's the combination in the far left, of dapa and

9   metformin, and there are the two individual

10   components. The blue row shows the difference

11   between the combination and the components. And

12   the combination was shown to be statistically

13   superior to each component. In particular, the

14   combination reduces HbA1c by about .5 percent,

15   compared to metformin alone. A planned secondary

16   analysis showed dapa alone to be non-inferior to

17   metformin alone. So you can see these values here

18   are quite similar.

19   Finally, these are the results for the

20   52-week glipizide-controlled study, which included

21   a total of 801 subjects in a primary analysis,

22   roughly 400 in each arm. Both arms showed an

1 almost identical reduction of .52 percent. The

2 estimated difference is zero, with a confidence

3 interval of negative .11 percent to positive .11

4 percent. This is well within the planned non-

5 inferiority margin of .35 percent. The margin of

6 .35 percent is generally consistent with FDA

7 advice.

8   So earlier, the applicant presented some

9 subgroup analyses. I conducted my own independent

10 analysis slightly differently. I just focused on

11 the six studies that I mentioned, that I most

12 closely reviewed, focusing on the following

13 subgroups, baseline HbA1c, which was a continuous

14 quantity; age dichotomized as over or under 65;

15 gender, race, and region. And, region, I was

16 interested in the U.S. and Canada combined versus

17 the rest of the world.

18   I also note, to increase statistical power,

19 when there are fixed-dose studies, I pooled the 5-

20 and 10-milligram doses. I did not include the

21 2.5-milligram dose, since the applicant hasn't

22 proposed to market that dose.

1   So in terms of the results, the monotherapy

2 study, the pioglitazone add-on study, and the

3 insulin add-on study all showed a stronger effect

4 of dapa in patients with higher HbA1c. In the

5 metformin add-on study, dapa was not effective in

6 patients 65 and older, and the trend was actually

7 in the wrong direction, favoring metformin alone.

8   The glipizide-controlled study showed a race

9 interaction, which is described in the next slide.

10 For gender and region, the interaction term was not

11 significant at the .05 level in any of the six

12 studies.

13   So as I mentioned, study 4 did show a

14 statistically significant interaction between the

15 treatment effect and race of .04. So this table

16 shows the change in baseline HbA1c by race and also

17 the differences between the two treatment groups.

18 We called it -- overall in this study, glipizide

19 and dapa showed virtually identical results.

20 However, there is perhaps a pattern here of

21 different efficacy by different racial groups, but

22 I did not observe this pattern in other studies.

1   Also, I noted earlier that the applicant

2   used last observation carried forward, or LOCF,

3   imputation for their primary analysis. When the

4   studies were initiated, this was consistent with

5   the advice that FDA was giving for diabetes

6   studies. In particular, FDA guidance has suggested

7   that LOCF would be conservative in the specific

8   sense that it would tend to underestimate the

9   effect of treatment in comparison to placebo.

10   More recently, there have been growing

11   concerns about LOCF in the statistical community

12   and more awareness that it is not conservative in

13   all cases. In response to these and other

14   concerns, FDA contracted with the National Academy

15   of Sciences to produce a report on handling of

16   missing data in clinical trials. This report came

17   out last summer, and it is critical of LOCF and

18   other single-imputation methods. For this reason,

19   I paid special attention to the sponsor's

20   sensitivity analyses and conducted my own. I agree

21   with the sponsor that dapa has an effect, but we

22   need a good estimate of the effect for benefit-risk

1   assessment.

2   I will focus on two of the sensitivity

3   analyses that the applicant submitted for a number

4   of studies. The first was an ANCOVA, analysis of

5   covariance, like the primary analysis, but only

6   using observed cases. So recall that the primary

7   analysis used LOCF, but unlike with the primary

8   analysis, for this analysis, no missing values were

9   imputed; that is, filled in.

10   Also, no observations were used once the

11   subject was given rescue medication. Each period

12   was analyzed separately, so once a subject was

13   rescued or dropped out, they were completely

14   excluded from the analysis. So this is all about

15   this first analysis.

16   The second analysis used a more complex

17   model called MMRM, which is also based on observed

18   cases and excluding observations after rescue, so

19   also excluding observations after rescue.

20   I will also show the results for a

21   sensitivity analysis that I conducted, which was

22   also an MMRM, as in here, but I used all available

1 observations for a subject, even if they were

2 rescued.

3 The fact that one sensitivity analysis that

4 I will show includes observations made after a

5 rescue may seem counterintuitive. After all, one

6 might reason that the subject's outcome becomes

7 irrelevant to the evaluation of the original

8 treatment once a rescue treatment is given.

9 However, the widely recognized intent-to-treat

10 principle says that the statistical analysis should

11 be based on the randomized treatment rather than

12 the actual, non-randomized treatment that a subject

13 received.

14 So, for example, the randomized treatment

15 for a subject might be dapa, 10 milligrams, and if

16 they were given rescue, then you could say that the

17 actual treatment was dapa plus rescue. From this

18 viewpoint, that is of the ITT principle. The fact

19 of rescue treatment should be disregarded. Once we

20 attempt to adjust for rescue in any way or exclude

21 the data, we are endangering the validity of the

22 analysis.

1   So this figure shows the results for the

2   primary LOCF analysis as well as the three

3   sensitivity analyses described on the previous

4   slide. I'm showing the results for study 2013,

5   which was the dapa and monotherapy study, and I'm

6   focusing on the comparison of the 10-milligram arm

7   to placebo.

8   The blue line shows the results of the

9   different analyses for the dapa arm; so these are

10   the blue lines here. You'll see the findings are

11   fairly consistent, that, basically, no matter how

12   you look at it, by week 24 -- so this is all at 24

13   weeks -- that there's a reduction in HbA1c of about

14   .9. So the more interesting part is actually these

15   pink lines here, because this shows what happens in

16   the placebo arm.

17   I should add, by the way, that no patients

18   were rescued in the 10-milligram dapa arm, which is

19   one reason why these lines are quite similar.

20   So looking at the placebo arm, furthest left

21   is the LOCF analysis, which is the primary

22   analysis. And you can see, by week 24, the

1   reduction in the placebo arm is .23 percent in

2   HbA1c. If you look at the ANCOVA analysis, you can

3   see it's quite different, that there's a reduction

4   of .62 percent in the placebo arm. However, I

5   should note that this analysis is particularly

6   favorable to the placebo arm because patients who

7   needed rescue are not included in week 24 at all.

8   The next one from the left, this one here,

9   is the MMRM analysis, which excludes post-rescue

10   observations. This shows a reduction of

11   .29 percent from baseline, which is not that

12   different from LOCF.

13   Finally, furthest right is the MMRM

14   analysis, which includes post-rescue observations.

15   This one shows a decrease of .45 percent from

16   baseline in the placebo arm.

17   This final analysis, which I prefer on

18   theoretical grounds, used an estimated effect that

19   is different from placebo, of .45 percent, or I

20   should say, negative .45 percent because it's less

21   than placebo. And I get .45 here because this is

22   roughly .9. I think it's .9, .91, and this is .45,

1   and the difference is .45. So here, we have .45 as

2   a treatment difference. In the primary analysis,

3   the treatment difference is .66.

4   So, in summary, these sensitivity analyses

5   suggest that LOCF may exaggerate the treatment

6   effect of dapa. And, of course, that was just one

7   study. This shows the results of my preferred

8   sensitivity analysis for the four placebo-

9   controlled studies, including the one I just showed

10   you. So, for example, in 2013, I showed a

11   treatment effect of .45 percent.

12   In each case, the analysis yields a smaller

13   estimated effect than the LOCF analysis, so you may

14   recall that the LOCF analysis for the 10-milligram

15   arm showed a treatment effect of dapa ranging from

16   .54 percent to .66 percent. You can see here it

17   ranges from .44 percent to .57 percent. I do note

18   that these are still statistically significant

19   effects.

20   So continuing with my sensitivity analysis,

21   here's the combination study. And, again, you can

22   see, in this case, the treatment effect is slightly

1   smaller than it was when it was shown from the LOCF

2   analysis.

3   Now, the sixth study I looked at was the

4   active controlled study with glipizide. In that

5   study, there was no rescue, so this issue is less

6   acute. I did conduct both an LOCF and MMRM

7   analysis, and they yielded similar results.

8   So I just went over the six studies that I

9   focused on. The applicant submitted reports for

10   four additional phase 3 studies, which had change

11   in HbA1c as a primary endpoint. There was an 11th

12   study that I'll discuss shortly that was concerned

13   with body weight and body composition.

14   Focusing on these four studies, the results

15   were generally consistent with those results from

16   the studies that I more closely reviewed, showing

17   evidence of efficacy for the 5- and 10-milligram

18   doses.

19   On the following slide, I'm going to show

20   you the results for all 10 phase 3 studies, which

21   had HbA1c as a primary endpoint. I'll add, the

22   only reported failed phase 3 study was in subjects

1   with moderate renal impairment. This study will be

2   discussed later in the presentation.

3   So this forest plot was provided by the

4   applicant, and it shows the 10 phase 3 studies,

5   which use HbA1c as the primary endpoint. LOCF is

6   used throughout. I'm just showing this as a quick

7   recap of all of the studies, the 10 phase 3 HbA1c

8   studies, including those studies I did not closely

9   review.

10   So the first six studies here show the

11   tested doses of dapa all beating the comparators,

12   as shown by the fact that all these confidence

13   intervals up to here exclude zero. The seventh

14   study, 2021, showed a combination of dapa

15   5 milligrams and metformin beating each component.

16   And the eighth study, study 2034, similarly showed

17   the combination of dapa 10 milligram and metformin

18   beating each component.

19   The second to last study showed dapa to be

20   non-inferior to glipizide, so that's why it's

21   around zero. And the last study shown is the

22   failed study in subjects with moderate renal

1   impairment. The results for all these studies are

2   shown for week 24, except for study C4, which used

3   week 52 for the primary endpoint. So that was the

4   glipizide-controlled study. So for the moderate

5   renal impairment study, the confidence intervals

6   include zero.

7   Now, I would like to draw your attention to

8   the issue of the durability of the treatment

9   effect. The applicant uses the term "maintenance,"

10   I believe, or "sustained efficacy," or something.

11   But I'm going to just stick to the word

12   "durability." The applicant raised this issue in

13   the briefing package.

14   Figure 15, shown here from the applicant's

15   briefing package, displays the change from baseline

16   at HbA1c out to week 102 for the metformin add-on

17   study. It is presented in the briefing package as

18   evidence of durability. And so, looking at

19   week 102, it does appear that this is a placebo arm

20   and these are the three active arms. It does

21   appear that there is a difference here that's

22   sustained. To the applicant's credit, however,

1   they showed how many subjects were used at each

2   time point, which I have highlighted with the red

3   box.

4   So the previous figure purports to show

5   evidence of durability. However, the sample size

6   does go down over time. For example, in the

7   placebo arm, you can see there, at week 102, only

8   21 percent of the subjects remain. They remained

9   or have either dropped out or have received rescue

10   medication. And even in the strongest dose, only

11   43 percent of the subjects remained. So you could

12   say that this sample has been enriched after

13   randomization. Based on this small selective

14   sample, any inference about durability is

15   questionable.

16   Now, we do acknowledge that the apparent

17   relationship between dose and dropout rate could be

18   taken as evidence as efficacy, so in other words,

19   the fact that, in the placebo arm, 21 percent

20   remain and in the 10-milligram arm, 43 percent

21   remain, one could certainly argue that's evidence

22   of efficacy. However, that does not show that a

given effect size was maintained all the way to the

end.

Figure 17 from the briefing packet also

raises the same issue. This is from the insulin

add-on study, and it shows a change in HbA1c out to

week 48. Again, there's an appearance that this is

the placebo arm and these are the other arms, that

there's a difference that's maintained to week 48.

And, again, to the credit of the applicant, they

have shown how many subjects are used at each time

point here.

In fact, you can see that in the insulin-

only arm, that is, the placebo arm, by the final

week in the figure, only 48 percent of the subjects

remain. Again, inference or estimation based on a

non-randomized subset of the starting population is

questionable. We believe that the best way to show

durability is by designing the study from the

beginning as a long-term study and maximizing

subject retention.

So I will now summarize my findings from the

primary endpoint. The applicant submitted 11 phase

1   3 studies, and I closely reviewed six of them.

2   These studies show that dapa is efficacious, both

3   as monotherapy and as an add-on therapy to a number

4   of anti-diabetic drugs. In other words, we have

5   seen strong evidence of a non-zero treatment effect

6   in a variety of settings.

7   For the purpose of benefit-risk assessment,

8   however, we need to be concerned about the actual

9   effect size. Due to substantial missing data,

10   there are divergent estimates for the actual effect

11   size. Based on the planned primary analysis, the

12   highest dose, 10 milligrams, reduces HbA1c by about

13   .5 to .6 percent -- perhaps, you could say

14   .7 percent in one case -- compared to placebo or

15   background therapy. Sensitivity analyses suggest,

16   however, that the effect size may be a bit smaller.

17   Finally, evidence presented for durability

18   in the applicant's briefing package should be

19   interpreted with caution. Please note that the

20   applicant has shown additional evidence for

21   durability in their presentation today, and we have

22   not had the opportunity to review that evidence

1   yet.

2   I will now discuss the secondary endpoints.

3   This slide briefly summarizes the results for

4   fasting plasma glucose, or FPG, I'll call it. As

5   with HbA1c, the placebo-controlled studies and the

6   combination study consistently show a treatment

7   effect.

8   So, for example, we can see in the four

9   placebo-controlled studies, the 10-milligram dose,

10   the effect ranges from about negative 17.5 to

11   negative 25; for the 5-milligram dose, from

12   negative 15.5 to negative 22. In the combination

13   study, dapa also beat each component in the effect,

14   and comparing the combination to metformin was

15   negative 25.5. I'm not showing the glipizide-

16   controlled study here because FPG was not one of

17   the key endpoints.

18   So this figure shows the results for weight

19   loss at week 24 of the four placebo-controlled

20   studies. I believe the applicant already showed

21   these results, so I'll just go over them briefly.

22   So the asterisks here indicate which arms

1   were different from placebo, statistically

2   different from placebo. So you can see, in the

3   monotherapy study, subjects at all arms lost

4   weight, but the dapa arms were not significantly

5   different. In the metformin add-on study, again,

6   all arms lost weight, but the dapa arms were

7   statistically different, yet different from

8   placebo. In the pioglitazone add-on study,

9   subjects in the pio arm gained weight and those in

10   the two dapa arms lost -- well, did not lose

11   weight, but they were essentially flat, which means

12   that they were superior to placebo. And then,

13   finally, the insulin add-on study, subjects in the

14   placebo arm did not appear to gain or lose weight,

15   while those in the dapa arm lost weight.

16   For the initial combination study, patients

17   on the combination therapy lost 3.3 kilos at

18   week 24 while those on the metformin arm only lost

19   1.4 kilos. So this is the combination versus

20   metformin alone, and this is a significant

21   difference. Dapa versus a combination was not

22   significantly different.

1   Finally, the glipizide-controlled study

2   subjects in the dapa arm lost 3.2 kilos at week 52,

3   while those on the glipizide arm gained 1.4 kilos,

4   which was a significant difference.

5   So I mentioned there were 10 phase 3

6   studies, which used HbA1c as a primary endpoint.

7   The eleventh study was a weight loss and body

8   composition study, and that used a change in total

9   body weight at week 24 as a primary endpoint. It

10   tested dapa as an add-on to metformin with 180

11   patients. As I said, the primary endpoint was

12   change in body weight. And the applicant reports

13   that subjects on the dapa arm lost about 3 kilos,

14   whereas those on the placebo arm lost about .9

15   kilos, so it was a difference of 2.08 kilos,

16   favoring dapa.

17   There was, however, a significant subgroup

18   interaction. There was a differential treatment

19   effect by gender. As you can see, there's a

20   significant interaction of .048 in weight loss by

21   sex. So you can see, for males, the net treatment

22   effect was that they lost an additional 2.8 kilos

1   if they were on dapa, whereas the females lost an

2   additional 1.2 kilos if they were on dapa.

3   So I previously mentioned a failed study in

4   patients with moderate renal impairment. So this

5   is the dedicated renal study. Patients had an eGFR

6   of 30 to 59; at least, that was the inclusion

7   criterion. This study did not show dapa to be

8   statistically better than placebo on either the 5-

9   or the 10-milligram dose. Moreover, the applicant

10   conducted what they describe as an ad hoc subgroup

11   analysis in which they looked at these stage 3a

12   patients with an eGFR of 45 to 59. And, again,

13   that subgroup analysis also failed to show a

14   difference from placebo.

15   So these are the results of the slide. So

16   you can see, in the entire study, there's just a

17   very slight difference for the two dapa arms of

18   about negative .1, not statistically significant.

19   For the stage 3a subgroup, for the 5-milligram

20   dose, it was a difference of negative .37, for

21   10 milligrams, negative .33. However, these doses,

22   this was not a statistically significant difference

1   from placebo.

2   So I'm now going to quote from this

3   applicant's background package, in which they

4   discuss this renal impairment issue. It states,

5   "When the stage 3a subgroup population, from the

6   special study" -- that is, the one I just showed

7   you -- "was analyzed for HbA1c effects of

8   dapagliflozin, 10 milligrams, the mean change from

9   baseline and placebo-corrected mean change from

10 baseline at week 24 were negative .33 and

11 .33 percent, respectively." So the key thing here

12 is that .33 percent I just showed you was a

13 difference from placebo.

14   "These mean changes were consistent with

15 changes evident in the larger pooled analysis."

16 I'll get to that in a moment. And then they

17 conclude, "Dapagliflozin was modestly effective in

18 patients with stage 3a moderate renal impairment."

19   So I would say that, in fact, statistically

20 speaking, the dedicated renal study does not

21 support this conclusion about the stage 3a subgroup

22 because the treatment effect was not statistically

1   significant in the subgroup. Note that even if the

2   results for stage 3a had been statistically

3   significant, this result would be viewed

4   skeptically, since the study failed in the primary

5   efficacy analysis. So in other words, when a study

6   does not succeed on the primary analysis, we are

7   usually skeptical of claims that are based on a

8   subgroup analysis.

9   The applicant also reports results of a

10   pooled analysis of patients from nine studies with

11   moderate renal impairment. They report that the

12   dapa 10-milligram dose had a significant effect at

13   24 weeks. However, we consider the dedicated

14   24-week renal study to provide a higher level of

15   evidence, so we have not reviewed this pool

16   analysis.

17   We note that the dedicated renal study had

18   about the same number of patients with moderate

19   renal impairment on the high dose of dapa as the

20   pooled analysis did. Therefore, there is no reason

21   to believe that the pooled analysis is giving a

22   more reliable estimate of the treatment effect.

1   So, in conclusion, a number of studies with

2   HbA1c as the primary endpoint show that

3   dapagliflozin is effective in patients with normal

4   renal function or mild impairment. Due to study

5   discontinuations and rescue, estimates of the

6   magnitude of the treatment effect do vary. The

7   LOCF estimate may overstate the effect. It should

8   be noted, however, that labels for currently

9   approved drugs do use LOCF. So LOCF results may be

10   informative for an apples-to-apples comparison.

11   The secondary endpoints were supportive. I

12   discussed the durability claims in the applicant

13   briefing package, which I found questionable.

14   However, I have not reviewed any additional

15   evidence that they showed today.

16   Finally, the dedicated study in patients

17   with moderate renal impairment did not show

18   efficacy. Thank you.

19   Now, I would like to introduce Dr. Somya

20   Dunn, who will be presenting the safety.

21   **FDA Presentation – Somya Dunn**

22   DR. DUNN: Hi. I'm Somya Dunn. I'm going

1   to be presenting the safety issues in

2   dapagliflozin. I'm going to begin with a brief

3   introduction on the drug. I'm also going to

4   discuss the PK profile in renal impairment, and

5   then I will focus on the safety issues for the rest

6   of the talk. These are some select safety issues

7   we'll discuss today: bladder cancer, breast

8   cancer, hepatic events, genital infections, urinary

9   tract infections, bone health, and cardiovascular

10   safety.

11   SGLT2 is a major transporter for renal

12   glucose reabsorption, and dapagliflozin is an SGLT2

13   inhibitor. It causes insulin-independent renal

14   elimination of glucose. The proposed indication is

15   adjunct to diet and exercise to improve glycemic

16   control in adults with type II diabetes. The

17   proposed dose is 10 milligrams, once daily. And

18   for patients at risk for volume depletion, such as

19   patients on loop diuretics, the proposed dose is 5

20   milligrams once daily. If approved, dapagliflozin

21   will be a first-in-class therapy.

22   The clinical program consisted of 26

1   pharmacology trials. There were 3 phase 2b trials

2   and 11 phase 3 trials. Cumulative exposure in the

3   phase 2b and 3 clinical trials at the time of the

4   NDA submission was 4,009 patient-years in dapa-

5   treated subjects and 1,682 patient-years in

6   controls. There were about two times more patients

7   exposed to dapa than to control.

8   You've already seen this forest plot,

9   presented by Dr. Norton. It summarizes that the

10   efficacy of dapa is better than placebo and

11   comparable to that of active controls. However, as

12   Dr. Norton emphasized, there is limited evidence of

13   efficacy in patients with renal impairment, which

14   is the last study on the forest plot.

15   In addition to the findings from the phase 3

16   study in patients with renal impairment, the

17   findings from this PK/PD study in patients with

18   renal impairment are also noteworthy. In this

19   study, a 20-milligram dose of dapa was given to

20   type II diabetic patients for -- it actually was

21   seven days. There was a three-day washout as part

22   of the 10-day course.

1   The Y axis in the graph depicts the area

2   under the curve of dapa exposure on day 10 after

3   the seven days of dosing for a 24-hour dosing

4   interval. The X axis shows four result columns,

5   one for healthy renal function, one for mild renal

6   impairment, one for moderate renal impairment, and

7   one for severe renal impairment.

8   As you can see, there are higher systemic

9   exposures in the patients with moderate and severe

10   renal impairment. The percent increase, which is

11   located at the top of the column, is compared to

12   type II diabetic patients with normal renal

13   function, which is the first column.

14   Despite the higher exposure in renal

15   impairment, there was a decrease in glucose

16   excretion. The Y axis here shows the cumulative

17   amount of glucose excreted in 24 hours at the

18   seventh day of dosing. Here, the bars on the

19   X axis are again labeled by renal function. You

20   can see the percent decrease in the cumulative

21   amount of glucose excreted when compared to the

22   type II diabetic patients that have normal renal

1   function, which is, again, the first column.

2   Now, I'm going to move onto the safety

3   discussion. Three main safety pools will be

4   discussed regarding the safety issues with dapa.

5   These were pools that were designated by the

6   applicant. One is the all-phase 2b and 3 studies

7   pool, which had short-term and long-term studies,

8   and the other two are placebo-controlled pools.

9   One is short-term studies only, and the other was

10 short-term and long-term studies. Most of the

11 long-term extensions ranged from about 24 to 78

12 weeks.

13   The first safety issue I'm going to discuss

14 is going to be bladder cancer. There were 7 cases

15 in dapa-treated male subjects in the phase 2b/3

16 pool reported at the time of the four-month safety

17 update. This was later updated as 9 cases in dapa-

18 treated patients and one in placebo.

19   The estimated incidence rates with updated

20 cases were as follows. There was an exposure of

21 3007 subject years in males in the dapa arms, and

22 this can be extrapolated to 299 cases per 100,000

1   subject-years. This can be compared to one case in

2   the control group during 1,697 subject-years in the

3   male control, specifically, and this can be

4   extrapolated to 59 cases per 100,000 subject years.

5   The rate ratio comparing dapa versus

6   controls in males was 5. This means that there is

7   a five times higher risk of bladder cancer in the

8   dapa-treated males. The confidence intervals are

9   wide and include 1, and it's important to note that

10 the trials were not powered to distinguish between

11 the incidence of bladder cancer in male dapa

12 subjects versus controls.

13   In their briefing package, the applicant

14 describes that all bladder cancer cases were

15 reported within two years of starting the study

16 drug. They also describe characteristics of the

17 patients that were diagnosed with bladder cancer

18 that are typical of patients that are diagnosed of

19 bladder cancer in general.

20   However, this table shows us that the

21 baseline bladder cancer risk factors in the phase

22 2b/3 pool were similar between the dapa-treated

1   patients and the controls. The first column are

2   the patients that were randomized to dapa. The

3   second is controls. And these are all risk factors

4   for bladder cancer, including hematuria at

5   baseline, smoking status, gender, race, history of

6   chronic cystitis, and use of cyclophosphamide.

7   At our agency, we had our epidemiology team

8   review these cases. The incidence of bladder

9   cancer was reviewed in the Surveillance,

10   Epidemiology and End Results database of the

11   National Cancer Institute. Literature was also

12   reviewed, and the rate for expected bladder cancer

13   was adjusted by 40 percent for type II diabetic

14   patients and was also adjusted for smoking and

15   other risk factors. A standardized incidence ratio

16   was calculated. This compares the observed

17   incidence of bladder cancer in dapa-treated

18   patients with expected incidence in age- and sex-

19   matched background population.

20   This table shows us the results of the

21   epidemiology study. You can see what was observed

22   in the clinical trials for dapa-treated patients

was 9 cases and what was expected, based on the

SEER data, were 3. What was observed in the

controls was 1 and what was expected was 2. The

standardized incidence ratio of observed versus

expected cases in males exposed to dapa was about

3, with a significant p value of .008.

Next, I'm going to discuss the breast cancer

cases. There were 9 cases observed in the female

dapa-treated patients versus none in controls in

the phase 2b/3 pool. Updated data from the sponsor

during the course of the review added an additional

case in controls. Estimated incidence rates with

the updated one case in the controls included an

exposure of 2,416 subject-years in female patients

in the dapa arms. This can be extrapolated to 372

cases per 100,000 subject-years, and for controls,

an exposure of 1,085 subject-years, this can be

extrapolated to 92 cases per 100,000 subject-years.

The rate ratio, comparing dapa versus

control in females, was 4, meaning that there is a

four times higher risk of breast cancer in the

dapa-treated females. Again, the confidence

1   intervals are wide and include 1. And, again, it

2   is important to note that the trials were not

3   powered to distinguish the incidence of breast

4   cancer in the female dapa subjects versus controls.

5   In these breast cancer cases, the applicant

6   describes in their briefing package that all cases

7   were detected within one year of exposure to dapa.

8   They also describe that there are clinical

9   attributes that are typical of patients that are

10   generally diagnosed with breast cancer.

11   This table shows us the breast cancer risk

12   factors at baseline for females in the phase 2b/3

13   pool. The first column are the patients that were

14   randomized to dapa. The second are the control

15   patients. This part of the table shows us body

16   mass index, body mass index categorization, age

17   categorization. This part of the table shows us

18   alcohol consumption, tobacco use at baseline, and

19   pre-randomization use of estrogen medication. The

20   rates are all similar between both groups.

21   I can go back, just to have you look at this

22   again.

1   Our epidemiology experts reviewed the

2 literature on breast cancer and type II diabetes.

3 Rates by age were compared to those seen in the

4 clinical program. By every age group, you can see

5 that the rates in the clinical trials are higher

6 for each group reviewed. These rates are given as

7 incidence rate per 1,000 person-years.

8   These populations are different, but this

9 comparison gives us a sense of what is described in

10 the literature and what was observed in the

11 clinical trials. Overall, the rates of both

12 bladder and breast cancer in dapa-treated patients

13 are higher than what would be expected.

14   Next, I'm going to talk about hepatic

15 events. I'm going to start this discussion by

16 describing the applicant's hepatic adjudication

17 report, which they also described during their

18 talk. This was submitted with the four-month

19 safety update.

20   There was a blinded adjudication process for

21 liver abnormalities. Three expert hepatologists

22 were on the adjudication committee. Criteria for

adjudication were elevations in AST or ALT,

including total bili, and these were beyond

specified -- prespecified thresholds, also liver-

related adverse events that led to discontinuation,

or liver-related serious adverse events, or adverse

events in any subjects who died. There were a

total of 54 adjudicated cases.

The clinical assessment of causality scale

consisted of five causal relationships: unlikely,

possible, probably, highly likely, or definite.

The committee found that there were 2 probable

cases, but once unblinded, these were both found to

be in control patients. They found 15 possible

cases. Once unblinded, 9 were in dapa-treated

patients and 5 were in controls. At the time of

review, one of these cases was still blinded.

We narrowed down the cases we focused on by

searching for Hy's law cases. Hy's law is a

threshold for liver enzyme tests that is indicative

of drug-induced liver injury. This occurs when

there is greater than three times the upper limit

of normal of AST or ALT, along with the greater

1   than two times the upper limit of normal of

2   bilirubin. There has to be no other clinical

3   explanation for the elevations.

4   In the phase 2b/3 pool, there were five dapa

5   cases that met the laboratory criteria for Hy's

6   law, both at the time of the NDA submission and

7   also at the time of the four-month safety update.

8   Liver experts at our agency were asked to review

9   these cases along with all the cases in the hepatic

10 adjudication report. They used the same causality

11 scale I already showed you, that was used by the

12 applicant's hepatic adjudication committee, and

13 they were asked to focus on these five cases in

14 particular. Using the same scale, they gave a

15 causality factor of three cases being unlikely.

16 One was ruled out as a drug-induced liver injury

17 and one case was thought to be probable.

18   This case has also been discussed by the

19 applicant, the case that was thought to be a

20 probable drug-induced liver injury case. I'm going

21 to discuss in more detail as well.

22   This was a 78-year-old male with a history

1   of several comorbidities that are common in

2   patients with type II diabetes. He was on

3   therapies that are common for these comorbidities,

4   including herbal supplements for GI discomfort. He

5   was on all these medications for at least 90 days

6   before beginning the study drug.

7   I want to go over his clinical course in the

8   next slide in more detail as well, but it's

9   important to note that the enzyme elevations did

10   not have a clear alternative explanation. Although

11   he was diagnosed with hemochromatosis during the

12   clinical course, this was not seen on biopsy. This

13   was a genetic diagnosis. His viral serologies were

14   negative. Although hepatitis C was not retested

15   during the clinical course, it was negative at

16   enrollment.

17   CMV and EBV acute titers were negative. He

18   did have generalized antibody elevations, but the

19   antibodies that are specific to autoimmune

20   hepatitis, which are listed in the last bullet

21   point, anti-liver/kidney microsomal type I, anti-

22   smooth muscle antibody, mitochondrial antibody, and

1   ANA, were negative.

2   This figure shows the time course of liver

3   tests for the patient. The elevations began around

4   day 85. Clinical signs were noted on day 196, and

5   the drug was actually stopped on day 192. The

6   clinical signs included some mild abdominal pain,

7   dark stool and urine, and the physician also noted

8   a "tinge of jaundice".

9   The elevations began to decrease after this

10   peak, around days 193 to 200, and the peak levels

11   are listed at the top of the graph. An ultrasound

12   done on day 213 was negative. A biopsy done on day

13   264 was consistent with either drug-induced liver

14   injury or autoimmune hepatitis, and the course of

15   prednisolone was started after the elevations had

16   begun to decrease on day 49. Again, this case was

17   reviewed in detail by our hepatic experts and was

18   characterized as a probable Hy's law case.

19   Marked elevations of 5 times and 10 times

20   the upper limit of normal display similar rates

21   between dapa and controls in the phase 2b/3 pool.

22   This table shows you elevations of AST 5 times and

1   10 times the greater limit -- the upper limit of

2   normal, and ALT of 5 times and 10 times greater the

3   upper limit of normal.

4   Per our FDA guidance document, one Hy's law

5   case in a clinical program is worrisome. Two are

6   considered highly predictive that the drug has a

7   potential to cause serious drug-induced liver

8   injury in a larger population. It has been

9   estimated that approximately 10 percent of Hy's law

10   cases progress to serious drug-induced liver

11   injury, for example, death or liver transplant.

12   In this case, there was one case in 2,489

13   patients that were exposed to dapa for at least six

14   months. That was at the time of the four-month

15   safety update. We can estimate that approximately

16   1 in 25,000 patients exposed for at least six

17   months may develop serious drug-induced liver

18   injury. It is difficult to make this estimate

19   based off of 1 case.

20   Next, I'm going to discuss genital

21   infections. Genital infections in the

22   dapagliflozin clinical program were mostly candidal

1   in nature.   The applicant used this terminology of

2   genital infections to classify.   Several preferred

3   terms were used to collect the events in this

4   category, including candidal-specific terms such as

5   vulvovaginal candidiasis.   Some were not specific

6   to candidiasis, such as pruritus.   Balanitis was

7   another preferred term used to find the incidence

8   of these events.

9   As you can see from the table, these events

10   appear to be dose related.   In the 10-milligram

11   group, we have 7 percent of patients having an

12   event.   In 5 milligrams, it was also 7 percent.

13   But in the 2.5-milligram group, it was only

14   5.8 percent.   This can be compared to placebo at

15   2.3 percent.

16   Second occurrence rates, when patients had a

17   second event, was higher in the placebo group than

18   in the dapa-treated patients.   This is included in

19   proposed labeling by the applicant.

20   The rates of genital infections were higher

21   in the female patients, in both the dapa and the

22   placebo group.   In the dapa-treated patients, there

were 10 percent of females and 3.5 percent of males that had these events.

Next, I'm going to discuss urinary tract infections. UTIs also occurred at a higher rate in dapa-treated patients. Again, several preferred terms were used to search for these events, including UTI and bacteriuria. As you can see, these rates do not appear to be dose related. The 10-milligram group had a 6.5 percent rate. The 5-milligram group had a 7.3 percent rate. The 2.5-milligram group had a 4.2 percent rate. And this is compared to a 4.5 percent rate in the placebo group. This was reported as a common adverse event in the clinical program.

The second occurrence rate was higher in the dapa-treated patients than in placebo. The rate of pyelonephritis was equal between placebo-treated patients and dapa-treated patients. And, again, this is included in proposed labeling. The rates were, once again, higher in the female patients for both dapa and placebo, 10 percent of females and 2.7 percent of males.

1   Next, I'm going to talk about bone health.

2 Dapagliflozin increases trabecular bone in rats,

3 causing greater bone mass density and strength at

4 high exposure multiples. Because of the unclear

5 significance of these findings, the applicant

6 followed fractures and markers of bone metabolism

7 throughout the clinical program. There were no

8 clinically significant changes in the laboratory

9 values in the short-term plus long-term pool, and

10 there was no pattern seen with the bone biomarker

11 changes in the five studies where these were

12 followed.

13   In terms of fracture rates, when we looked

14 at the short-term placebo-controlled pool and

15 focused in on an analysis of normal renal function

16 patients, there was an imbalance in the rate, .6

17 percent of patients in the dapa-treated group

18 versus .2 percent in the placebo-treated group.

19   However, when we looked at the entire short-

20 term pool, this imbalance was not noted, .4 percent

21 occurring in the dapa-treated patients versus .7

22 percent in the placebo-treated patients. The

1 numbers before are just the numbers of event

2 fractures.

3   In the placebo-controlled short-term and

4 long-term pool, we also did not see an imbalance,

5 with an equal rate in both groups, and fragility

6 fracture rate in the dapa-treated subjects versus

7 placebo was also very similar. These are

8 osteoporotic fractures.

9   In the renal impairment study, we had

10 52-week data that, again, showed us an imbalance.

11 In the 10-milligram group, 8.2 percent of patients

12 had an event of fracture, 3.6 percent in the

13 5-milligram group, and there were none seen in the

14 placebo group. There were negligible lab value

15 changes associated with these imbalances.

16   In the placebo-controlled short-term pool,

17 looking at the moderate renal dysfunction patients,

18 which are patients of the same renal dysfunction as

19 the renal impairment study, we did not see this

20 imbalance.

21   All of this data was reviewed by the

22 metabolic bone disease team at the FDA in the

1 Division of Reproductive and Urology Products.

2 They also looked at the bone mineral density that

3 was submitted with the body weight and composition

4 study, which is the only study that followed this.

5 We had 50-week data to look at. Two-year data are

6 pending. Minimal effects were seen on bone mineral

7 density. And, overall, it was thought that there's

8 no indication at this time of dapa effect on bone

9 loss or fracture.

10   The last safety issue I'm going to discuss

11 is cardiovascular safety. There was a meta-

12 analysis conducted by the sponsor in 14 trials.

13 The prespecified primary composite endpoint

14 consisted of the following adjudicated events:

15 cardiovascular death, myocardial infarction,

16 stroke, and hospitalization for unstable angina.

17   There were a total of 6,228 subjects in the

18 database. Seventy-eight subjects had a primary

19 endpoint event. There were two trials that did not

20 have any events at all. Forty-eight events

21 occurred in the dapa-treated subjects and 30 events

22 occurred in comparators.

1   The primary endpoint analysis shows us that

2   the upper bound of the 98 percent confidence

3   interval is 1.18. The p value for assessment of

4   heterogeneity of the studies was .92. This tells

5   us there's no significant difference in the event

6   rate across the trials, which is a zero percent

7   heterogeneity. The component endpoints of MACE

8   were also consistent across the trials.

9   We concluded that there is no increased risk

10   of cardiovascular events that occurs with the use

11   of dapa over control.

12   This forest plot shows us the event rate for

13   each individual study is low. The red studies are

14   add-on studies, black are monotherapy, and blue are

15   combination studies. The confidence interval

16   either crosses 1 or is on 1 in three of the

17   studies, but, overall, there is a consistent

18   pattern of not showing excess risk. The applicant

19   has proposed a cardiovascular outcomes trial to

20   show the benefit of dapagliflozin.

21   So, overall, there were higher rates in the

22   dapa-treated patients of bladder cancer, breast

1 cancer, genital infections, and urinary tract

2 infections. Of particular concern were the cancer

3 cases. There was one probable case of Hy's law.

4 Bone health is being monitored in an ongoing study,

5 and the meta-analysis in cardiovascular safety

6 showed us there was no increased cardiovascular

7 risk. And we know that the applicant has a

8 dedicated cardiovascular study proposed. Thank

9 you.

10 **Clarifying Questions from Committee**

11 DR. THOMAS: Thank you for the presentation

12 from the FDA. We'll now take clarifying questions

13 from the committee for the FDA. Please raise your

14 hand, and we'll call you as identified. While

15 people are doing that, I'd like to ask a question

16 of Dr. Norton.

17 In your slide that you talked about the

18 comparison of using last observation carried

19 forward versus a mixed model of using subjects who

20 are rescued, you felt that the rescue group

21 analysis was the most conservative -- most

22 conservative may not be the right word, but the

1   most appropriate.

2   It doesn't seem to make much sense to me

3   because, in this study, there was a very small

4   number of dropouts, unlike what we see with

5   obesity. The effect that we see should carry over

6   at the time of the duration of the study.

7   If you add the placebo arm and you use

8   rescue therapy, as to the analysis, you should get

9   a diminishment in the difference between placebo

10   and your treatment group, because, theoretically,

11   depending on how you rescue them, you could

12   actually even have a beneficial effect of placebo

13   over treatment.

14   So I actually thought last observation

15   carried forward would be more conservative, and

16   using the rescue after the analysis would actually

17   not be the most appropriate, and biased.

18   DR. NORTON: Yes. This is John Norton.

19   I'll take that in a couple of parts. First of

20   all -- so, yes. There is an argument that I think

21   I even acknowledged, that there is a sense that,

22   well, if someone was rescued, doesn't that mean

1   that they -- that somehow shouldn't be seen as a

2   measure of the efficacy after they've been rescued.

3   As I discussed in the briefing package, it's

4   a little tricky at that point because the person

5   who was rescued differs from other people in two

6   ways. One, they were eligible to be rescued, so

7   they're different in that way. And the other way

8   is, of course, they got the actual biological

9   effect of the rescue. So it's very difficult to

10   really disentangle those two things. But I am

11   certainly sympathetic to that argument, and it's

12   one I've certainly heard.

13   The other issue in terms of conservatism,

14   well, if you define conservatism as I did, in terms

15   of does it -- if a conservative analysis is

16   something that makes the test agent look like

17   placebo, then in this case, LOCF was not

18   conservative in the sense that the other approaches

19   all showed a smaller effect, and LOCF showed the

20   largest effect. But I guess it depends on what

21   your reference point is. Perhaps, there's

22   something that's less conservative than LOCF.

1   The other issue is that there's also an

2   issue of what -- so it depends on what you would

3   predict would happen without treatment over time,

4   in the sense that if you think that the natural

5   tendency is for people to get worse over time, then

6   in that sense, LOCF may appear to be conservative.

7   However, as we saw in the actual trials,

8   essentially, even in the placebo, people were

9   improving over time so that, in that sense, LOCF

10   was not conservative.

11   DR. THOMAS: Dr. Veltri?

12   DR. VELTRI: Yes. Thank you. This question

13   refers to the FDA slide 12 on safety, bladder

14   cancer in particular. You compared risk factors in

15   the total population, but it seems as though the

16   numerical discrepancies are driven entirely by the

17   males. So my question is, if you just looked at

18   the male populations, did that have any effect on

19   these potential risk factors for the development of

20   bladder cancer?

21   DR. DUNN: Yes. Are you saying that this

22   table is for the whole pool and not just for the

1   males?

2   DR. VELTRI: That the ends seem to suggest

3   that they're there for the whole pool, but I don't

4   know that to be the case. But since it was a

5   finding in the males, was there anything in the

6   baseline that was more predictive, potentially, in

7   that gender?

8   DR. DUNN: As the applicant had pointed out,

9   there were some patients that had a baseline

10   hematuria. And if you look at the individual

11   cases, it does appear that there might have been

12   some predisposition of those patients' history of

13   smoking and this history of hematuria.

14   However, we do not have a table comparing

15   just the male patients in this pool to see if there

16   was a baseline difference. This, as you're

17   pointing out, is for the entire phase 2b/3 pool,

18   where we don't see the differences. But assuming

19   that everything was randomized appropriately, which

20   is what we can assume from seeing this table, we

21   could assume, potentially, that that would be

22   balanced between the male patients as well.

1   DR. THOMAS: Dr. Hendricks?

2   DR. HENDRICKS: This is two questions for

3   Dr. Norton. One question is, I'd like to go back

4   to sponsor's slide 10, if we could.

5   So, Dr. Norton, in talking about efficacy,

6   about dapa, you said that the effect on the

7   hemoglobin A1c is 0.5 to 0.6, but it might be less

8   than that. And in looking at this slide, we see

9   that 0.5 or 0.6 would compare favorably with some

10 of the other medications that have been approved

11 previously and are in use now.

12   So I'm wondering, have you looked at any of

13 these other medications using the same statistical

14 type of analysis?

15   DR. NORTON: No, I have not. This is the

16 only medication that I'm personally familiar with

17 in terms of the efficacy.

18   DR. HENDRICKS: The second question is, I

19 guess I don't understand your slide number 10 --

20   DR. NORTON: My slide number 10?

21   DR. HENDRICKS: -- your slide number 10,

22 talking about the treatment effect interacting with

1   race.

2   So do I understand the slide correctly?

3   There's less of an effect in the whites as opposed

4   to minority groups?

5   DR. NORTON: Yes. That would be correct.

6   So you can see -- so I'll just summarize again.

7   So, overall, there was an interaction with race.

8   If you look at the individual groups here, we have

9   white, black or African-American, Asian, and other.

10   And as I mentioned, the overall effect was for the

11   two treatment groups to be the same. So if there

12   was no race affected at all, you'd expect all these

13   differences to be zero on average.

14   So why there was a bit of a trend for dapa

15   to be positive, that is worse, but compared to the

16   standard, there's a very tiny trend. And it does

17   appear that, yes, for the black African-American

18   population, the Asians, that the trend was

19   apparently for dapa to work better. But, again,

20   that's not -- those individual findings are not

21   statistically significant. It's simply the net

22   interaction between race and effect.

1   DR. HENDRICKS: So you did not see this in

2   the whole group or in any of the other subsets?

3   DR. NORTON: Right. I mean, I just went

4   through the other -- I'm not sure what you mean by

5   the other subsets, but I went through the other

6   studies, and I didn't see any sort of consistent

7   pattern of one race group doing better than other

8   race groups.

9   DR. HENDRICKS: Thank you.

10   DR. THOMAS: Dr. Kaul?

11   DR. KAUL: Thank you. I have two questions.

12   The first question is for Dr. Dunn.

13   How would you characterize the

14   cardiovascular risk profile of patients enrolled in

15   this clinical development program? How does it

16   compare with some of the recent programs such as

17   GLP-1 agonist and DPP-4 inhibitors? And in your

18   opinion, does it run consistent with the diabetes

19   cardiovascular guidance document?

20   DR. DUNN: It does run consistent with the

21   guidance document. The upper bound of the

22   confidence interval is 1.18, which is well below

1   the 1.8 that was needed for filing of the NDA.

2   DR. HENDRICKS: But the question I had was

3   referring to the cardiovascular risk profile, the

4   baseline risk profile. Is it consistent with what

5   is recommended in the cardiovascular risk

6   development guide?

7   DR. DUNN: This was conducted in a meta-

8   analysis, which was just the generalized type II

9   diabetes population that had the general

10   cardiovascular risks that you would find in that

11   population. The dedicated study that the applicant

12   will be conducting, that study will be in high-risk

13   patients, and that will be, potentially, if the

14   drug is approved, post-marketing. That would run

15   post-marketing.

16   In terms of other drugs, I'm going to defer

17   to him.

18   DR. IRONY: Yes. Dr. Kaul, I think, in

19   general, it's comparable to the other recent drug

20   development programs for GLP-1 that were recently

21   approved. As you saw from the applicant's

22   presentation, they enrolled a wide range of the

1   diabetic population from the newly diagnosed,

2   younger patient populations with a very low risk of

3   cardiovascular disease to elderly people, including

4   the people in the dedicated renal trial, renal

5   impairment trial. So there was like a wide range.

6   The event rates were somewhat lower than

7   what we would expect at 2 percent, of an annual

8   event rate or so, both for dapagliflozin and for

9   control. But, overall, it's not completely out of

10   range from other recent trials in type II diabetes

11   for other development programs.

12   DR. SVANBERG: If it would considered

13   helpful, we have the breakdown for the

14   cardiovascular risk factors, if that would help the

15   committee in the discussion.

16   DR. THOMAS: If you have it and you can

17   present it briefly, go ahead.

18   DR. SVANBERG: Dr. List will present that

19   data.

20   Dr. List?

21   DR. LIST: Yes. Briefly, the patients in

22   the overall program, about 60 percent of them had

1   hypertension. And these are balanced risk factors

2   between dapagliflozin and control. About 60

3   percent had a medical history of hypertension;

4   50 percent with hyperlipidemia. Forty percent were

5   current or former smokers. About 20 percent had a

6   history of prior cardiovascular disease. Age is a

7   factor. About 20 percent of the population was

8   greater than or equal to age 65. Family history of

9   premature coronary artery disease was in about

10   15 percent of patients. And then if you consider

11   renal impairment as a risk factor, about 11 percent

12   had an estimated GFR less than 60.

13   DR. THOMAS: Thank you.

14   Dr. Gregg?

15   DR. GREGG: Sure. I had two questions, one

16   for Dr. Norton and one for Dr. Dunn.

17   For Dr. Norton, I was wondering whether you

18   could clarify what proportion of the patients

19   actually had imputed data due to the LOCF. And,

20   secondly, whether that was -- it stands to reason

21   that that would be more common among those with

22   some renal failure than not because they're more

1   likely to go into rescue therapy.

2   Then my question for Dr. Dunn was, in

3   computing the expected cases for the bladder cancer

4   and the breast cancer, you had to make an

5   assumption that diabetes carries an excess risk,

6   which means you had to pick a point estimate from

7   meta-analysis, which there's not great consensus

8   around what that point estimate is, I don't think.

9   And I'm curious how much -- if you were to apply

10   some variation to what that assumption is, how much

11   affects the relative risk.

12   DR. NORTON: Yes. I'm afraid -- in terms of

13   how many values were actually imputed in each data,

14   I don't have those numbers offhand, so I'd like to

15   defer to the sponsor.

16   DR. SVANBERG: We have the number and the

17   proportion of subjects with imputed values. I'll

18   ask Dr. Henry to address the question.

19   Dr. Henry?

20   DR. HENRY: David Henry, biostatistics,

21   Bristol-Myers Squibb. For most studies in the

22   dapagliflozin group, there were roughly 12 to 15

1   percent that were imputed. For most of the placebo

2   groups, it was 25 to 27 percent. In the renal

3   study, the placebo group had 40 percent, and it was

4   around 25 percent for the dapa groups.

5   DR. THOMAS: Thank you.

6   DR. DUNN: For your question regarding the

7   safety, I'm going to defer the question to

8   Dr. Hampp, who is the epidemiologist.

9   DR. HAMPP: Thank you for your question. I

10 used an imputation of 40 percent increase

11 associated with diabetes. The meta-analysis

12 indicated 48 percent increase, and we weighted to

13 include that. The control group in the meta-

14 analysis were non-diabetics. But in our case, the

15 control group was SEER, as the general population,

16 some of whom are diabetic. So I used 40 percent,

17 and I acknowledge that there is variation in

18 estimates across studies.

19   However, the studies included in the meta-

20 analysis that did adjust for smoking had a general

21 agreement in that magnitude in studies that were

22 published since, which is in the last four years,

1   also had magnitudes that were similar. Still

2   there's uncertainty in the estimate.

3   How it affects the relative risk estimates;

4   if you take the SEER background estimates that I

5   calculated, you divide them by 1.4, that would

6   assume no increase. If you want to have a maximum

7   sensitivity estimate of 2, you would divide by 1.4

8   and multiply by 2 to get a maximum there.

9   I cannot produce the numbers now in this

10   moment, but there is some uncertainty, but the

11   difference would remain.

12   DR. THOMAS: Dr. Piantadosi?

13   DR. PIANTADOSI: Thank you. My question is

14   for Dr. Dunn. Earlier, I asked the sponsor about

15   rate ratios -- and I'm referring specifically now

16   to bladder and breast cancer -- and Dr. Wei from

17   Harvard told us that there were some zero

18   denominators that made it unreasonable or

19   impossible to calculate rate ratios with precision.

20   Now, we learn from your presentation,

21   perhaps somewhat unfortunately, that there are no

22   longer zero denominators in your comparator group.

1   There's one case each of breast and bladder cancer.

2   And we are able to determine rate ratios, those

3   being approximately 5 and 4, according to what you

4   presented. I wonder -- also, there seem now to be

5   nine cases of each cancer, if I remember the slide

6   you presented correctly.

7   Can you tell us the process by which we got

8   from zero denominator in your comparator group and

9   seven cases, which I think the sponsor presented

10   this morning, to nine versus one? What's the

11   process that either found additional cases or

12   adjudicated those cases?

13   DR. DUNN: For bladder cancer, we did find

14   out, at the time of the four-month safety update,

15   about the seven cases that were in the male

16   subjects in the phase 2b/3 pool. We didn't know

17   about that at the time of the NDA submission.

18   We had asked the sponsor to send in

19   expedited reports for these cancer cases, and we

20   received an additional three cases approximately

21   maybe a month after the four-month safety update.

22   And the sponsor can maybe clarify what their

1   process was in getting those reported. But that

2   was what happened with the bladder cancer.

3   With the breast cancer, the nine cases that

4   were observed were given to us initially with the

5   NDA submission. The one additional case in

6   controls, we probably just found out about within

7   the last month or so. It's pretty recent. So,

8   again, maybe the applicant can tell you their

9   process in those cases.

10   DR. SVANBERG: Dr. List will address how we

11   have reported these cases for bladder and breast.

12   Dr. List?

13   DR. LIST: So cancer, and the question about

14   breast and bladder cancers, emerged relatively late

15   in the phase 3 program. In the NDA filing, we had

16   five bladder cancers, all on dapa, and nine breast

17   cancers, all on dapa. At the four-month safety

18   update, that became, as explained, seven bladder

19   cancers and nine breast cancers, all on dapa, none

20   on control at the four-month safety update.

21   With request from regulatory authorities,

22   including the FDA for more information on the

1   bladder cancers, we unblinded three subsequent

2   bladder cancers. That gave us nine bladder cancers

3   on dapagliflozin and one on control. Because this

4   was an evolving signal, we took another look at our

5   data in May of this year. The data sweep for the

6   four-month safety update was in October of last

7   year. So we took a look in May of this year, and

8   that's what brought the additional one breast

9   cancer case, to bring that to nine cases, to one

10   for breast cancer.

11   So that's how it's evolved, and we've been

12   analyzing this as an evolving safety issue to bring

13   the most current data to bear.

14   DR. PIANTADOSI: So is it safe to say, then,

15   that apart from the vagaries about hematuria, and

16   possible prevalent cases, and so on, that you

17   outlined earlier, that the sponsor and the FDA have

18   agreed that those, as of this moment, are in fact

19   the correct numbers? There's no dispute about

20   whether these are appropriate cases to include and

21   be considered in this deliberation?

22   DR. IRONY: I think it's fair to conclude

1   that those are the correct numbers, but I would

2   defer to the applicant to give their opinion.

3   DR. SVANBERG: We concur with that

4   conclusion, nine cases on dapa from bladder and

5   breast, respectively, and one on comparator for

6   breast and bladder, respectively.

7   DR. PIANTADOSI: Thank you.

8   DR. THOMAS: Dr. Capuzzi?

9   DR. CAPUZZI: Yes. My question was along

10   the same lines that have, I think, been partially

11   answered but not completely. If there is a cancer

12   signal here, it's important, and might go beyond

13   just these two organs. The typical person that has

14   bladder cancer will just present with a self-

15   limited episode of bright red hematuria, which the

16   patient may or may not remember later on.

17   With breast cancer, here again, that's not

18   something we take in lightly. There should be some

19   systematic way of either doing this by imaging or

20   somehow to follow that. And, indeed, a patient

21   might forget that they had a hematuria. What about

22   the bladder cancer that doesn't bleed? And that is

1   a sporadic-type thing.

2   So these are very soft numbers, and, yet,

3   it's a very important issue, and I'm not

4   comfortable with it.

5   DR. THOMAS: Dr. McBryde?

6   DR. SVANBERG: So in order to put that in

7   perspective, maybe we can offer the view of

8   Dr. Dean Bajorin to put this in the perspective of

9   diagnosis.

10   DR. THOMAS: I think we can if it's concise,

11   because we have a few more questions for the FDA.

12   Go ahead.

13   DR. SVANBERG: Dr. Bajorin?

14   DR. BAJORIN: Dean Bajorin. I'm a medical

15   oncologist specializing in bladder cancer, and I'm

16   a paid consultant by BMS. I will direct my answer

17   to your issue with regard to bright red blood.

18   There actually is a very pivotal study that's done

19   in the United States, by Ed Messing and colleagues,

20   actually looking at screening for hematuria, in

21   which trace and above was considered of importance.

22   Then they screened those patients with

1   regard to whether or not they had infections, et

2   cetera, to play a role in the hematuria, and then

3   went on to examine them according to the guidelines

4   by the AUA and EUA, which included imaging and

5   included cystoscopy. An important fact, most of

6   those patients did not have gross hematuria, and in

7   that patient population, the incidence of bladder

8   cancers was 4.7 percent.

9   So not all patients present with gross

10   hematuria. We see it very frequently, but I think

11   the issue of trace and above is really important

12   with regard to evaluating the disease, and we could

13   add more later on.

14   DR. THOMAS: Thank you. Dr. McBryde?

15   DR. MCBRYDE: Thank you. This is a question

16   for Dr. Dunn. I'm just curious, in your safety

17   analysis, if you had looked at the hypovolemia and

18   renal events. One of the main things that I was

19   looking at, a published manuscript of, I think, a

20   phase 2b MB102009, they actually had written in the

21   report that there was an episode of acute renal

22   failure in the dapa-treated group, with concomitant

1   treatment, with furosemide, and enalapril,

2   diuretic, and an ACE inhibitor.

3   With the previous comments from the sponsor,

4   about 60 percent of the enrolled subjects had

5   hypertension, there was no data that I could find

6   in the studies about concomitant drug therapy. But

7   certainly in the diabetic population, angiotensin-

8   converting enzyme inhibitors and angiotensin

9   receptor blockers are very widely used and

10   diuretics are commonly used as first-line therapy

11   for hypertension.

12   So one of my concerns is the risks of acute

13   renal failure. According to the sponsor's packet,

14   it appears to have been included as dehydration as

15   an adverse event and not acute renal failure,

16   though the manuscript states differently.

17   So I was curious if you had done an analysis

18   that wasn't presented in here, looking at the risks

19   associated and whether or not there are increased

20   risks associated with the use of diuretics or the

21   renin-angiotensin-aldosterone system antagonists.

22   DR. DUNN: At this time, the analyses that I

1   have are the ones that were conducted by the

2   applicant. I don't have additional analyses in

3   those specific populations that you're bringing up.

4   My backup slide number 6 for the clinical backup

5   slides, again, these are presented by the

6   applicant. But the events of volume depletion,

7   which were defined as hypotension, hypovolemia, and

8   dehydration, were reported in more patients treated

9   with dapa than comparator. This is in the placebo-

10   controlled pool.

11   As you point out in the study -- we can go

12   to slide 7. In study 29, which is the moderate

13   renal impairment study, when the applicant combined

14   those moderate renal impairment patients with the

15   moderate renal impairment patients from the

16   placebo-controlled pool, there is a higher rate of

17   renal or volume status AEs I'm seeing in these

18   subgroups of patients than in the general placebo-

19   controlled pool. But, again, I don't have analyses

20   specific to background therapies and so forth.

21   I'm not sure if the applicant has any

22   additional analyses.

1   DR. SVANBERG: Yes. We do have the

2   information on the events reported, renal events,

3   and I'll ask Dr. List to provide that.

4   DR. LIST: So we've looked at the renal

5   events in our program and at the volume events in

6   our program, and there is some overlap in these

7   events. The way we've done this is we've taken

8   spontaneously reported adverse events and looked by

9   the preferred term from the MedDRA dictionary, and

10   lumped all of the renal events together, lumped all

11   of the volume-type related events together, and

12   that's where we come up with these sorts of

13   numbers.

14   When we look into the more severe events,

15   look at specifically serious adverse events, that

16   is medically important events or events requiring

17   hospitalization, et cetera, for both of these

18   types, there are four on dapagliflozin and four on

19   control, so it's quite balanced.

20   The one case that you are referring to in

21   study 009, which is an add-onto-insulin pilot

22   study, is actually a case that, because of the way

1   it was report and the preferred term used, fell

2   into the volume bucket as opposed to the renal

3   bucket. But that case is a case where the patient

4   experienced dehydration and pre-renal azotemia and

5   was treated with oral fluids.

6   With respect to the renal serious adverse

7   events, of the four that are on dapagliflozin, one

8   was actually an error in calculation of creatinine

9   clearance, but it got reported as a serious adverse

10   event and went into our database like that, even

11   though it wasn't acute renal failure. We also had

12   one case that was renal failure in the setting of a

13   hospitalization in a patient who was very complex,

14   who had CHF exacerbation and pneumonia, and

15   ultimately died.

16   One case, the third case, of these was a

17   patient who had urinary obstruction, leading to the

18   renal failure, and that was cured with relieving

19   the urinary obstruction through catheterization.

20   The fourth one is a patient in the dedicated

21   study in moderate renal impairment, who's a

22   patient, who had a gradual decline in the renal

function and a very serious adverse event of renal

failure with worsening renal insufficiency.

DR. MCBRYDE: If I could follow up on that,

did you have a pre-defined definition for acute

kidney injury, either using something similar to

the RIFLE criteria, the risk injury failure, or the

AKIN, the Acute Kidney Injury Network definitions?

I'm curious as to how much of a change in

creatinine clearance, or estimated GFR, or serum

creatinine would trigger it being a renal event

versus a volume event.

DR. LIST: We did not have a definition of

acute kidney injury that we used in the program.

What we did have in the program is we had cutoffs

in all of the studies for discontinuation of

patients, based on changes in serum creatinine or

in estimated creatinine clearance. And if a

patient's discontinued for a laboratory event, that

is required to then also be reported as a clinical

adverse event. And that's where we then gather all

of these data from the spontaneously reported

clinical adverse event.

1   The other thing we looked at is that we

2   looked at patients whose serum creatinine increased

3   from their baseline to one and a half over

4   baseline. And we also looked at patients whose

5   serum creatinine increased to an absolute value of

6   2.5 milligrams per deciliter. For both of these

7   thresholds of elevations of serum creatinine, we

8   see no difference between dapagliflozin and

9   control, and very, very few patients actually hit

10   that 2.5-milligram-per-deciliter threshold.

11   DR. MCBRYDE: If I could just ask one last

12   clarification, were you using creatinine clearance

13   by measured or estimation? I've heard previously

14   that you were using eGFR, using, I presume, the

15   four variable MDRD formula. So I'm just curious

16   what criteria you're using across all these studies

17   to evaluate renal function or dysfunction.

18   DR. LIST: The main way that we've looked at

19   renal function across the entire program is by

20   serum creatinine measurements and the estimations

21   that are based on those. So that's Cockcroft-Gault

22   creatinine clearance and estimated GFR. And when

1   we've looked at it, whichever the three ways you

2   look at it, the findings are concordant. We have

3   measured creatinine clearance only in the earlier

4   studies, the phase 2 and earlier studies as we were

5   exploring doses. And it requires to measure the

6   creatinine clearance at 24-hour urinary collection,

7   which is hard to do accurately in a phase 3

8   program.

9   DR. THOMAS: Dr. Kaul?

10   DR. KAUL: Thank you. I have two questions.

11   One is a follow-up to Dr. Dunn, and then there's

12   one quick question for Dr. Norton. The mean

13   duration of diabetes in this developing program is

14   about six years and there is increasing evidence to

15   suggest that the longer the duration of diabetes

16   may be necessary to increase the risk to a CHD

17   equivalent. In fact, there's a recent study

18   published in the archives in March from a British

19   regional heart study that CHD risk was only

20   observed when the diabetes duration was greater

21   than eight years.

22   So how many of these patients had diabetes

duration greater than eight years in this study?

DR. DUNN: I'm sorry. I actually don't have

the breakdown of the cardiovascular risk, but I

think the applicant did have something that they

had presented. I'm not sure if they have that.

DR. SVANBERG: We do not have that

information for the totality of the program. The

insulin study subjects had had diabetes for

approximately 10 years, and we can look into it

over the break, if we can get it for the totality

of the program.

DR. KAUL: Then one question for Dr. Norton.

Your conservative estimate of the effect size of

hemoglobin lowering, A1c lowering, of .45 percent,

is not very materially different from what the

sponsor's primary analysis revealed. But the

benefit-risk estimate that they presented was based

on how many patients reached the glycemic threshold

or glycemic target of less than 7 percent. Your

analysis is unlikely to impact that.

Is that a fair statement?

DR. NORTON: It depends. It depends on how

1   they computed it. I don't know how. I guess, if

2   patients were rescued or there was no follow-up, if

3   they were counted as failures, then -- I'm not sure

4   how they -- I'll leave it up to the applicant. I'm

5   not sure how they conducted their analysis.

6   DR. SVANBERG: I will ask Dr. Parikh to

7   address how the patients were rescued and how that

8   was managed.

9   Dr. Parikh?

10   DR. PARIKH: So we did that analysis and we

11   showed that analysis because of the issue of

12   patients dropping out, long term, and issues with

13   LOCF.

14   Can I have slide 38, please, the slide from

15   my color presentation? This is an analysis of

16   patients switching to a target of less than

17   7 percent. I'm not a statistician. This is close

18   to ITT analysis. It includes all patients at all

19   time points. Any patient who was discontinued from

20   the study for any reason or any patient who had

21   beta missing was considered to be a treatment

22   failure in this. And, therefore, was a failure,

and did not achieve 7 percent. So this reflects

the patients who achieved 7 percent in a more ITT-

like fashion.

DR. SVANBERG: I do apologize for my

oversight on the previous questions. We do have

the duration of diabetes in subgroups. I'm not

sure if 1080 (ph) is the denominator or it might be

10 years.

Can we get that slide back, please?

DR. THOMAS: Actually, can -- because I have

a few other questions before you finish up.

Would you be able to prepare that, and we

can present that in the afternoon.

DR. SVANBERG: We can absolutely do that.

DR. NORTON: Yes. I just wanted to briefly

comment. So, yes. If you accept the 7 percent

cutoff the way they've defined it as an appropriate

measure of benefit, then -- I mean, if it's an

appropriate measure of benefit than it is in

some -- yes, in that sense, my analysis would be

less relevant.

DR. THOMAS: Dr. Strader?

1   DR. STRADER: This question is for Dr. Dunn.

2   It's the same question that I asked the applicant.

3   Does the FDA have a protocol that they

4   recommend for applicants with respect to evaluating

5   hepatotoxicity of the agents that they are

6   studying, or do you just review the cases as

7   they're sent to you at the individual updates and

8   gather the data to determine whether there's a

9   hepatotoxicity?

10   DR. DUNN: We don't have a protocol; we have

11   a guidance.

12   Dr. Avigan?

13   DR. AVIGAN: Hi. I'm Mark Avigan. So the

14   answer is that we use the information that's

15   provided to us. And it's pretty much codified in

16   the guidance that was published in 2009. And the

17   basic point is that we use differential diagnosis

18   with all the exclusions, looking at the highest

19   cases in particular for causality, and those then

20   serve as sentinels, with a potential of the drug to

21   cause idiosyncratic hepatotoxicity in a large

22   exposure population. And you heard the discussion

1   about the differential diagnosis and the

2   probabilistic analysis.

3   DR. THOMAS: Dr. Seely?

4   DR. SEELY: I wanted to know if the FDA had

5   reviewed urinary microalbuminuria data from the

6   sponsor, and if so, what your feelings were about

7   that.

8   DR. DUNN: No. We have not reviewed that

9   data in detail. I don't think that I reviewed that

10 data. I don't recall seeing it.

11   DR. SVANBERG: We have evaluated

12 microalbuminuria in the program, and that forms

13 part of the dose (indiscernible). I'll ask

14 Dr. List to address the findings.

15   Dr. List?

16   DR. LIST: When we look at the totality of

17 the data that we have, most of the patients don't

18 have microalbuminuria, so it's not very informative

19 regarding that. What is informative is when we

20 look in the dedicated study in moderate renal

21 impairment, where there is a substantial proportion

22 of patients with microalbuminuria and some patients

1   with macroalbuminuria.

2   Within that study, if you look at the change

3   from baseline, there is a decrease in albuminuria,

4   measured by the urinary albumin to creatinine ratio

5   in a spot sample, for patients who receive

6   dapagliflozin compared to placebo.

7   We've also looked in that study at a

8   categorical shift analysis. We've looked across

9   the entire program of the categorical shift

10   analysis, but it's not very informative since most

11   patients are normal at baseline. But within that

12   study, where a significant portion are not normal

13   at baseline and you look for people, did they shift

14   worse? That is, did they go from normal to

15   microalbuminuria or micro to macro, or did they

16   shift better, from macro to micro or micro to

17   normal?

18   What we see is, taking the 10-milligram dose

19   as an example, 5 got worse, 16 got better. That's

20   compared to placebo, where 10 got worse and 7 got

21   better. This is by no means conclusive evidence of

22   an effect on albuminuria, but it is hypothesis

1   generating, that there could be something

2   beneficial.

3   DR. THOMAS: We will now break for lunch.

4   We will reconvene again in this room in one hour

5   from now, at 1:10 p.m. Please take any personal

6   belongings you may want with you at this time. The

7   ballroom will be secured by FDA staff during the

8   lunch break.

9   Panel members, please remember that there

10   should be no discussion of the meeting during lunch

11   amongst yourselves or with any member of the

12   audience. Thank you.

13   (Whereupon, at 12:06 p.m., a luncheon recess

14   was taken.)

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1   A F T E R N O O N   S E S S I O N

2   (1:12 p.m.)

3   **Open Public Hearing Session**

4   DR. THOMAS: Good afternoon. Both the Food

5 and Drug Administration and the public believe in a

6 transparent process for information gathering and

7 decision making. To ensure such transparency of

8 the open public hearing session of the advisory

9 committee meeting, FDA believes it is important to

10 understand the context of an individual's

11 presentation.

12   For this reason, FDA encourages you, the

13 open public hearing speaker, at the beginning of

14 your written or oral statement, to advise the

15 committee of any financial relationship that you

16 may have with a sponsor, its product, and, if

17 known, its direct competitors. For example, this

18 financial information may include the sponsor's

19 payment of your travel, lodging, or other expenses

20 in connection with your attendance of the meeting.

21 Likewise, FDA encourages you, at the beginning of

22 your statement, to advise the committee if you do

1   not have any such financial relationships.

2   If you choose not to address this issue of

3   financial relationships at the beginning of your

4   statement, it will not preclude you from speaking.

5   The FDA and this committee place great importance

6   in the open public hearing process. The insights

7   and comments provided can help the agency and this

8   committee in their consideration of the issues

9   before them.

10   That said, in many instances and for many

11   topics, there will be a variety of opinions. One

12   of our goals today is for this open public hearing

13   to be conducted in a fair and open way, where every

14   participant is listened to carefully and treated

15   with dignity, courtesy, and respect. Therefore,

16   please speak only when recognized by the chair.

17   Thank you for your cooperation.

18   The first speaker will be Kelly Close.

19   MS. CLOSE: Good afternoon, Chairman Thomas,

20   members of the committee, and FDA officials. I am

21   the editor in chief of three diabetes and obesity

22   publications that serve patients, providers, and

1   those who research and develop therapies to treat

2   these conditions.

3   Our mission is to help improve patient

4   outcomes by delivering the best information

5   possible to everyone who needs it. By way of

6   disclosure, while various manufacturers subscribe

7   to our news service, Closer Look, this group does

8   not include Bristol-Myers Squibb or AstraZeneca,

9   the sponsors of dapagliflozin. Our patient

10   newsletter, diaTribe, is free and does not accept

11   advertising.

12   I have had diabetes since I was a teenager.

13   I'm glad for all patients with diabetes, including

14   myself, especially myself, that therapies have

15   improved so much in the decades since I was

16   diagnosed, albeit from a low base. But we have

17   reached a pivotal crossroads.

18   In the last two years, three drugs have been

19   turned down for diabetes, one of them twice. Two

20   drugs have been approved for diabetes with the same

21   mechanism as a drug already on the market. Three

22   drugs have been turned down for obesity, the cousin

1   of diabetes. And since FDA's decision in 2008 to

2   require cardiovascular outcome trials, the cost to

3   develop drugs for diabetes have increased by an

4   estimated $100 million per compound.

5   For most people with type II diabetes, no

6   available therapy by itself or in combination with

7   others can achieve target levels of glycemic

8   control for more than a few years without

9   substantial risks. But we are encouraged that,

10   today, we are here to discuss a drug with a new

11   mechanism of action. We continue to look forward

12   to new mechanisms of reducing blood glucose that do

13   not cause weight gain or hypoglycemia.

14   Furthermore, we are encouraged by the

15   potential of this mechanism to be combined,

16   eventually, with other classes of drugs to produce

17   a potentially superior outcome for patients. As a

18   reminder, I know, as a patient, no drugs today are

19   disease modifying and I do hope to see that in my

20   lifetime.

21   Also, I'm cheered today to see a drug with a

22   cardiovascular profile that suggests it could even

1   be cardioprotective, given the reassuring point

2   estimate and confidence intervals from the pre-

3   approval outcome assessments.

4   Simpler drugs are easier for patients to

5   take and for doctors to prescribe. If there were

6   ever a time that better and easier drugs were

7   needed, that time is now, given the shortage of

8   doctors and nurses to treat diabetes and given the

9   serious adherence problems that we all read about

10   frequently.

11   You, of course, will assess all of the risks

12   of dapagliflozin using your own clinical and

13   scientific expertise with the help of your

14   colleagues and those, importantly, with a

15   particular specialization in assessing cancer risk

16   and drug-induced liver injury. We, of course,

17   would urge you to recommend the appropriate

18   labeling and risk management to address the safety

19   signals that have been raised. No drug will ever

20   be zero risk.

21   I'm reminded of that constantly as a

22   patient. I would just ask, please mitigate the

1   risk while being open to further treatments that

2   could help people with diabetes now, whether this

3   involves a narrow label, rigorous post-marketing

4   follow-up, and/or conditional approval based on

5   further safety and efficacy assessments.

6   We ask members of the advisory committee and

7   FDA to consider how their actions can affect

8   innovation. More than anything, we ask the FDA to

9   promote public health and foster innovation by

10   trying to be even more consistent and predictable

11   in its recommendations and decisions.

12   The agency's mission includes the

13   challenging but very important goal of balancing

14   regulation with innovation. While we want to

15   ensure the safety of diabetes drugs, we also

16   believe ongoing innovation is critical. Although

17   we don't want to make cardiovascular outcome trials

18   the focus of our words today, we do want to note

19   that at the annual American Diabetes Association

20   meeting in late June this year, we were

21   disappointed to hear a CDER deputy director use the

22   number of IND filings and even the number of

1   phase 2 meetings to state that CV guidelines have

2   had no effect on any patient in the diabetes field.

3   Since there is at least a 5- to 10-year lag

4   between investment in discovery stage assets to IND

5   filings, and even longer to phase 2 meetings,

6   broadly speaking, we would note that it would be

7   helpful if FDA could identify measures of

8   innovation that assess more immediate impacts of

9   FDA guidelines.

10   As discussed already today, the available

11   class of drugs carry with them a range of side

12   effects. The durability of treatment is very

13   variable. Many agents are using combination

14   regimens. And even if you find the right

15   combination, it is hardly time to celebrate. Most

16   of these drugs work well for a relatively short

17   period of time, at best five years, and assume very

18   good adherence, which we know is not the reality

19   any of us is living.

20   We badly need more and better options. The

21   drugs need to be safe and effective, but they don't

22   need to be perfect. They do, however, need to be

1   available, even if in some limited form initially,

2   if we are ever going to curb an epidemic that is

3   spiraling out of control.

4   Through extensive study of the diabetes

5   field, I'm convinced that the relative abundance of

6   type II drugs, while a wonderful demonstration of

7   the success of research in the field, does not

8   satisfy patient and public health needs in this

9   mechanistically complex progressive disease.

10   One more sentence, please. We need

11   continued research and development in this area.

12   We ask FDA to be aware of their roles, in both

13   encouraging and potentially discouraging

14   investment.

15   On a final note, from a patient perspective,

16   I wish every patient could see how hard FDA and the

17   advisory committees work, and I thank you all from

18   the bottom of my heart for all of your work on this

19   front in helping patients. Thank you.

20   DR. THOMAS: Thank you for your comments.

21   The next speaker at the public hearing will

22   be Diana Zuckerman.

1   DR. ZUCKERMAN: Thank you. I'm Dr. Diana

2   Zuckerman. I'm president of the National Research

3   Center for Women and Families, and I'm here

4   speaking on behalf of the Center and our cancer

5   prevention and treatment fund.

6   Our center is dedicated to improving the

7   health and safety of adults and children, and we do

8   that by examining research and translating the

9   results of that research into usable information

10   for policymakers, for patients, and for the general

11   public. And our non-profit center does not accept

12   funding from pharmaceutical companies, so I have no

13   conflicts of interest.

14   I'm here today, speaking from my perspective

15   as someone trained in epidemiology at Yale Medical

16   School. I also was on the faculty at Yale and at

17   Vassar and conducted research at Harvard, and

18   currently I'm a fellow at the Center for Bioethics

19   at the University of Pennsylvania. So I'm putting

20   together all of those perspectives, as well as

21   having worked for the Department of Health and

22   Human Services, and also being the daughter of my

1   dad, who has diabetes. So I'm also speaking from

2   the patient perspective today.

3   My concern about this drug, dapa, is that

4   there are just too many unanswered questions. And

5   I have testified at FDA meetings before, but I

6   don't remember any drug that had quite such serious

7   unanswered questions as this one does.

8   So when we look at safety and we think about

9   the liver toxicity, those are unanswered questions.

10   I don't know what the safety issues are for the

11   liver, but we certainly would want to know more

12   before the drug is approved.

13   Obviously, what really stands out is the

14   possibility that this drug could increase the risk

15   of breast cancer, bladder cancer, and potentially

16   other cancers as well. And I just want to mention

17   in passing that my father got diabetes at the age

18   of 90 after being treated for prostate cancer with

19   Lupron, which is considered potentially a risk

20   factor for diabetes. So wouldn't that be ironic,

21   that he gets diabetes because of his cancer

22   treatment, and then could go on this drug and get a

1   different kind of cancer? I think you would all

2   agree that that's not the kind of innovation we're

3   looking for.

4   It is always exciting when a new drug comes

5   along that has a different mechanism of action that

6   might possibly be very helpful. It could add to

7   the different treatments available to patients.

8   And in an ideal world, doctors and patients would

9   know the research, and look at it carefully, and

10   make a determination about what's best for each

11   patient. But in the real world, that just doesn't

12   happen very often.

13   So we do need to be concerned about what

14   kind of informed consent patients would have. And

15   it's impossible to have informed consent when the

16   research hasn't been done, but there are these very

17   frightening possibilities of increased cancer risk.

18   And I'm sure that everybody at this table knows

19   that since cancer usually takes years to develop,

20   it's very unclear what's going on with this drug.

21   Are these cancers -- did they occur by chance or

22   are they related to taking the drug?

1   But we also know from hormone replacement

2   therapy research that even in the short term,

3   exposure to certain hormonal activity and other

4   drug effects can increase the risk of breast

5   cancer, in particular in the short term, not just

6   over the long term. But we would certainly want

7   more research to find out if this effect is even

8   stronger over a period of time or if it disappears

9   entirely.

10   So what I would ask you to consider is that

11   although this drug seems promising, we don't really

12   know very much about the efficacy. We know that

13   it's very good for glycemic control for some

14   patients, but we don't know how that affects their

15   actual health over time. We know that other

16   diabetes drugs have been found to be very good for

17   glycemic control, but not necessarily improve

18   health.

19   So we have the efficacy question that's not

20   completely answered and a lot of risk questions

21   that haven't been answered at all. And I would ask

22   you to consider the importance of answering those

1   questions before this drug is approved and sold,

2   because once it's on the market, it would be used

3   very widely by many people, some of whom

4   potentially could be very harmed by it.

5   One other thing I just want to mention is

6   even though we do want more drugs to treat diabetes

7   and to help patients, we're not in an emergency

8   situation. We don't have to rush this drug to

9   market. It makes a lot of sense to wait until

10   we've answered these very important safety

11   questions. Thank you very much.

12   DR. THOMAS: Thank you for your comments.

13   The next speaker is Sidney Wolfe.

14   DR. WOLFE: Thank you. I do not have any

15   financial conflicts of interest. We can all agree,

16   as has been said several times, it's worth

17   repeating, first, of a new chemical class of agents

18   for type II diabetes. It also is the first drug to

19   act as the sodium glucose transport protein, SGLT2.

20   But their request for approval is based solely on

21   surrogate efficacy in terms of lowering A1c, and

22   there is no evidence of any improved clinical

1   outcomes, as opposed to an older drug like

2   metformin.

3   So the overall question as the FDA phrased

4   it is the efficacy of dapa needs to be balanced

5   against safety signals identified in the clinical

6   trials. And there are a large number, including

7   bladder cancer, breast cancer, one probable Hy's

8   law hepatotoxicity case, increased genital and

9   urinary tract infections, chronic osmotic diuresis

10   every time you take the drug with hypovolemia, and

11   risk of dehydration, and, I would add, heat

12   intolerance, especially in older people who are

13   using diuretics.

14   The baseline characteristics of the risk

15   factors for bladder cancer in the two groups was

16   really similar, as pointed out this morning. The

17   nine dapa bladder cancer cases amounted to 299 new

18   cases, as opposed to 59 for the control group, per

19   100,000 patients. The incidence rate ratio between

20   active control and treatment was 5.08 with a two-

21   sided p value of .15, not statistically

22   significant, but then the trials were not powered

to pick up a statistically significant difference.

Based on the SEER data, though, only three cases of bladder cancer, not nine, would have been expected in the male dapa-exposed population. The standardized incidence ratio observed versus expected was 2.98. As pointed out, that's a p value of .008.

Breast cancer. The breast cancer risk factors at baseline were also similar between the two groups, but the age-specific incidence rates of breast cancer were higher than those reported in the literature. It could be a safety signal that dapa may be associated with increased risk of breast cancer.

This was stated this morning, but it can't be stated too much. I knew Hy Zimmerman very well. Finding one Hy's law case in the clinical trial database is worrisome. In this case, there was a probable case of mild, to moderate, to severe dapa-induced liver toxicity. Recent examples of drugs causing hepatotoxicity, such as bromfenac, troglitazone, ximelagatran illustrate that

1   predicted value of Hy's law, where findings during

2   clinical trials were noted and severe drug-induced

3   liver injury occurred after marketing.

4   FDA staff expressed concerns about the

5   completeness of the database concerning

6   hepatotoxicity, both in terms of dropouts of

7   subjects and in incomplete database, looking at all

8   these serial liver values.

9   Genital and urinary tract infections,

10 significant increases in the total of vulvovaginal

11 yeast infections and vaginal infections with all

12 dapa patients, 2.4 percent compared with placebo,

13 .5. And these are just the ones where they're

14 actually infections, not the larger group you saw

15 this morning.

16   Urinary tract infections significantly

17 increased in all dapa patients, 4 percent compared

18 with placebo patients, 2.7 percent. Again, as

19 mentioned, events related to chronic intermittent

20 osmotic diuresis, an increase in volume depletion

21 events, .7 percent in the dapa group, .4 percent in

22 the control group. Dapa also increases the

1   hematocrit, which could be a risk factor for

2   cardiovascular events.

3   Summary. For a drug offering only a new

4   mechanism of A1c lowering, devoid of any evidence

5   of clinical benefit, the long list of FDA's serious

6   concerns quoted below are used strongly against

7   approving dapa. I mentioned the concerns before.

8   Approving dapa would amount to treating a

9   surrogate marker of a disease by increasing the

10 risk of other actual diseases. On the other hand,

11 the precautionary principle, which would be not

12 approving dapa, would be a public health move in

13 the right direction at a time when we do have a

14 number of other drugs available, some of which

15 actually have a clinical benefit. Thank you.

16 **Questions to the Committee/Committee Discussion**

17   DR. THOMAS: Thank you for your comments.

18   The open public hearing portion of this

19 meeting has now concluded, and we will no longer

20 take comments from the audience. The committee

21 will now turn its attention to address the task at

22 hand, the careful consideration of the data before

1   the committee, as well as the public comments.

2   At this time, we'll have some additional

3   questions from the panel, and before that starts,

4   I'd like the sponsor to come up and present some

5   data from an earlier question of Dr. Kaul's.

6   DR. SVANBERG: Thank you. We would like to

7   address the question which came before the break

8   around the duration of type II diabetes in the

9   patients in the program.

10   If I can have slide 1312, please. Based on

11   the overall dapagliflozin program, we had already

12   divided the data in subjects who had had diabetes

13   for less than 3 years, 3 to 10 years, greater than

14   10 years. In response to the request was a

15   specification of longer duration than eight years.

16   We have added that at the very end as well.

17   The data here show that a total of

18   30 percent, approximately, of patients in the

19   program have had diabetes for more than eight

20   years. Twenty-two percent have had diabetes for

21   more than 10 years.

22   Does that answer your question, Dr. Kaul?

1   DR. KAUL: Yes. And have you ever done a

2   subsidiary analysis stratifying the cardiovascular

3   event rate, according to the duration of diabetes?

4   Does that have an impact on it?

5   DR. SVANBERG: Dr. List will address that

6   question.

7   Dr. List?

8   DR. LIST: Yes. If I may have slide 45-1,

9   please, we've looked at the primary cardiovascular

10   outcome endpoint by a number of subgroups. The

11   duration of diabetes is right in the middle. We

12   don't have the cut at the eight-year cut. We have

13   this cut that we talked about with the 3 years and

14   10 years as the two cut points. There, all three

15   of those groups show point estimates that are

16   consistent with the overall results from the

17   composite and primary endpoint.

18   DR. THOMAS: Thank you.

19   We will now go back to questions that were

20   left over from this morning, but if you wish to ask

21   a question now, please raise your hand so we can

22   recognize you. Dr. Capuzzi?

1   DR. CAPUZZI: Am I to understand that there

2   are no more presentations from the sponsor? Is

3   that correct?

4   DR. THOMAS: That's right. You had a

5   question this morning for the sponsor?

6   DR. CAPUZZI: Yes. Okay. Well, one thing

7   that I'd be interested in is, I haven't seen a

8   slide on the structure of the compound, how it's

9   bound, how it travels in plasma, what's the T one-

10   half, the biotransformed. And all of these are

11   issues which have a bearing on its potential risk-

12   benefit profile and possible potential. I don't

13   want to dwell on neoplasms, but, you know, it's an

14   issue that has not been resolved and talked about.

15   But I think that tells you an awful lot

16   about the drug, if you could show what it looks

17   like, unless I missed it. And it's not in the

18   reading material here.

19   Is that possible to do or is that out of

20   order?

21   DR. THOMAS: Do you have a slide of the

22   actual structure?

1   DR. SVANBERG: We do have a slide of the

2   structure of dapagliflozin. We have slide 17-3.

3   And I will at the same time ask Dr. Boulton to come

4   up and address the question, how the drug is

5   metabolized and distributed.

6   DR. CAPUZZI: That's water insoluble, is it

7   not?

8   DR. SVANBERG: Sorry?

9   DR. CAPUZZI: That's certainly water

10   insoluble, is it not?

11   DR. SVANBERG: Dr. Boulton?

12   DR. BOULTON: David Boulton, clinical

13   pharmacology, BMS. Just to answer your question

14   about the solubility, actually, it is highly water

15   soluble, greater than the usual dose; would

16   dissolve in 10 mls of water.

17   DR. CAPUZZI: Is it protein bound?

18   DR. BOULTON: The protein binding of dapa is

19   91 percent.

20   DR. CAPUZZI: How does it work? How is it

21   biotransformed?

22   DR. BOULTON: Can I have slide 6-17, please?

1   So on the left-hand side, we have the parent

2   molecule: dapagliflozin. It is mainly metabolized

3   through UGT1A9 to a 3-0 glucuronide metabolite.

4   It's a stable ether metabolite. Sixty percent of

5   dose is transformed to this particular metabolite.

6   The other metabolites are glucuronide metabolites,

7   which are minor, and also some phase 1 oxidative

8   metabolites, which are also very minor.

9   DR. CAPUZZI: Excuse me, but what are the

10   therapeutically active medications in that, or

11   subspecies, if you know?

12   DR. BOULTON: We believe that the major

13   therapeutic moiety is the parent dapagliflozin.

14   DR. CAPUZZI: Excuse me? Of the parent

15   drug?

16   DR. BOULTON: Parent drug, yes.

17   DR. CAPUZZI: I see. And the T one-half of

18   it, about?

19   DR. SVANBERG: The half-life of the drug is

20   approximately 12 hours.

21   DR. CAPUZZI: Twelve hours? Okay. All

22   right. Thanks.

1   DR. THOMAS: Dr. Felner? Dr. McBryde?

2   DR. MCBRYDE: If I could just get that same

3   slide back, I did have a question.

4   What is known about dapa's excretion from

5   the kidney? Is it freely filtered, the glomerulus?

6   Given that high protein binding, I would be

7   suspicious that it's secreted by the proximal

8   tubule. And so I'm curious about competitive

9   inhibition with other drugs, particularly

10 furosemide that was mentioned earlier.

11   I also wanted to ask if you had any data on

12 the effects of hypoalbuminemic states, such as

13 commonly seen in patients with chronic kidney

14 disease, and what the impact of macro to overt

15 macroalbuminuria and overt proteinuria may be with

16 regards to the bioavailability of dapa in the brush

17 border of the S1/S2 segments of the proximal

18 convoluted tubule.

19   DR. SVANBERG: So if I captured your

20 questions correctly, the first question was related

21 to dapagliflozin and its excretion through

22 filtration in the kidney?

1   DR. MCBRYDE: Correct.

2   DR. SVANBERG: The second question was

3   relating to its interference, if any, with a loop

4   diuretic?

5   DR. MCBRYDE: Just as an example, in terms

6   of other drugs that we know are either excreted or

7   blocked proximal tubular secretion of drugs, like

8   the H2 blockers.

9   DR. SVANBERG: And the third question was

10 relating to how potential proteinuria impacts the

11 bioavailability of the drug?

12   DR. MCBRYDE: Correct.

13   DR. SVANBERG: I will ask Dr. Boulton to

14 address the questions.

15   Dr. Boulton?

16   DR. BOULTON: So, first of all, with regards

17 to urinary excretion of dapagliflozin, about

18 2 percent of dose is recovered as unchanged dapa in

19 urine. And when you look at the free fraction

20 filtered relative to the amount, the unbound renal

21 clearance is fairly similar to GFR. So we think

22 it's mainly freely filtered.

1   With regards to interactions with other

2   active transporters, dapa is a PGP substrate. We

3   have done a drug-drug interaction with digoxin,

4   which is a well-known PGP substrate and marker of

5   activity. We see no interaction there. We have

6   not conducted a study with H2 blockers

7   specifically, but our in vitro transporter studies

8   would suggest there's very little potential for

9   active transporter base drug-drug interactions.

10   DR. MCBRYDE: Haven't you done any studies

11   in hypoalbuminemic states or proteinuric states to

12   look at the effect on the activity of dapa on the

13   SGLT2 transporter? I'm asking just because we see

14   the phenomenon of furosemide resistance with

15   proteinuric patients due to tubular binding of the

16   free drug to luminal proteins. And given the high

17   protein binding of dapa, one of the concerns I was

18   wondering is, with this reduction in responsiveness

19   with decline in GFR, could there also be problems

20   with proteinuric states inducing a resistance to

21   dapa.

22   DR. BOULTON: We have not specifically

1   studied that population from a pharmacokinetic or

2   pharmacodynamic perspective.

3   DR. MCBRYDE: Thank you.

4   DR. THOMAS: Dr. Smith?

5   DR. SMITH: Right.   So carrying on with the

6   issue of the biochemistry here, do we know whether

7   this drug undergoes glucuronidation solely in the

8   liver, or does it get glucuronidated in the kidney,

9   a site of substantial activity of UDP glucose

10   dehydrogenase?   This could certainly impact the

11   biological activity of the drug, and it could

12   potentially explain the divergence between those

13   individuals with normal GFR and those renally

14   impaired.

15   DR. SVANBERG: Based on the data from our

16   phase 1 studies, these data suggest that

17   glucuronidation of dapagliflozin takes places both

18   in the liver and in the kidney.

19   DR. SMITH: Second issue has to do with

20   trying to put into perspective the potential risk

21   for bladder carcinogen -- neoplasia with the drug.

22   The issue is what do we know about the endogenous

1   small molecules and xenobiotics that might be

2   co-transported by the glucose sodium transporter

3   that would be inhibited by dapa and could, at least

4   theoretically, result in concentration of an agent

5   in the urine?

6   DR. SVANBERG: Dapagliflozin has not shown

7   carcinogenistic (ph) potential, and I will ask

8   Dr. Reilly to present that data.

9   Dr. Reilly?

10   DR. SMITH: My question has nothing to do,

11   necessarily, with the carcinogenesis of the

12   molecule itself, but what reabsorption is blocked?

13   What potential molecules are remaining in the urine

14   and presented to the bladder as a result of the

15   putative action of the drug?

16   DR. SVANBERG: I am sorry. I misunderstood

17   the question. Dr. Reilly has picked up on it and

18   will address it.

19   Dr. Reilly?

20   DR. REILLY: Tim Reilly, drug safety and

21   evaluation, Bristol-Myers Squibb. If I understand

22   your question correctly, you're just looking for

1   what sort of ions under the materials would be,

2   perhaps, concentrated in the face of dapagliflozin

3   in the urine. We've done an evaluation of

4   whether -- so there are glucose and sodium ions,

5   for instance, that are concentrated in the urine.

6   With the diuretic effect, that are increases in

7   calcium ions, for instance.

8   Those effects occur in animal studies just

9   as they occur in humans, and we see no evidence, in

10   our studies nor in the literature, that increases

11   in glucose, or sodium, or calcium, would lead to an

12   increased risk.

13   DR. SMITH: There are other possibilities,

14   though. What about small proteins that could be

15   co-transported along with glucose?

16   DR. REILLY: We've not specifically looked

17   at the variety of things that, perhaps, could be

18   suggested. But, again, based upon the mechanism

19   and the activity of dapagliflozin in preclinical

20   species, we do see the very things that occur in

21   humans occur in animals at more robust effects than

22   would occur in the human setting, and we see no

1 evidence of those things. So for instance, we do

2 see an increase in protein output in the urine, in

3 animals, and in the face of that, we see no

4 evidence of any risk, no hyperplastic changes, nor

5 any tumors.

6   DR. SMITH: But that certainly could be a

7 consequence of animal to human inequity, right?

8   DR. REILLY: If I understand where you're

9 going with this, you're going with, perhaps, the

10 predictivity of the animal studies for the human

11 setting.

12   DR. SMITH: I mean, that's just in response

13 to your rejoinder to me.

14   DR. REILLY: Fair enough. So if I may

15 respond to that. So from our reading of the

16 literature and our consultation with outside

17 experts, we're not aware of any bladder carcinogen,

18 human bladder carcinogen that does not cause some

19 effect in animals.

20   Whether they be tumors or they be

21 hyperplastic changes, we see no evidence of either

22 one of those with dapagliflozin at enormous

1   multiples of the human exposure. So we believe

2   that the data are very strong to the effect that

3   there is no evidence to suggest that there would be

4   a mechanism-related effect.

5   On that front, there's also no evidence,

6   based upon what's available in the literature,

7   around the mechanisms of bladder carcinogenesis,

8   that dapagliflozin causes any of those effects. So

9   for instance, a variety of xenobiotic agents cause

10   cytotoxicity or irritation type effects. They

11   cause inflammatory-type responses. They cause

12   other such changes that have been related to the

13   cause of bladder carcinogenesis, and we see none of

14   those things occur with dapagliflozin.

15   DR. THOMAS: Thank you.

16   Dr. Savage?

17   DR. SAVAGE: Thank you. As I read the

18   material and then heard the discussion today,

19   there's sort of a broad question, and I'll give you

20   one example of it that's come up. And that's that

21   I really wonder if there are adequate members of

22   individuals in some of the subgroups to get a good

1   sense of how valuable this drug will be. It's

2   obviously an interesting mechanism.

3   But the example I wanted to give is that

4   this drug could be useful in elderly patients,

5   maybe enabling them to stay off of insulin and

6   reduce their risks of having hypoglycemia and so

7   forth. But elderly patients tend to have a

8   decrease in renal function. And it's not clear to

9   me, from looking at some of the numbers, that you

10   have that many people above 65, and certainly above

11   75, that have been evaluated.

12   So that given the fact that there are going

13   to be millions of diabetic patients out there that

14   are in that age group, and that it could be

15   particularly beneficial for that age group because

16   it could make it easier to control their diabetes,

17   can you comment on the adequacy of the sample

18   sizes, not only for the over-65, but older people

19   also, to assess the magnitude of the benefit you

20   get from using this drug?

21   DR. SVANBERG: Thank you. The dapagliflozin

22   program contained 1200 subjects who were older than

65. And I will ask Dr. Parikh to address the

efficacy, as it was evaluated in this subgroup.

Dr. Parikh?

DR. PARIKH: So we had about 20 percent of

our patients over the age of 65 across phase 3, as

was mentioned. In the subgroup analysis that we

did, specifically we tried to get in as many

patients as possible that gives us a placebo

comparison, so that we could power for interaction

testing in that particular subgroup.

But if you want to look at magnitude of

effect, it's perhaps best that we look at the

studies which had more elderly patients and compare

dapa and how we did versus other drugs.

Of the 1200 patients, more than 600 came

from three trials, the add-on to met versus

sulfonylurea trial, the add-on to SU trial, and the

add-on to insulin trial.

If I can have slide 25-10, please? This

slide summarizes what we saw in subgroups of

patients with age over 65 in dapa versus placebo.

In the top row is active comparison versus SU.

1   There are about 100 patients in each of the

2   treatment arms about age 65. The effect of dapa

3   was .48 percent in that particular group. For SU,

4   it was .6 percent. It is known, about SU and its

5   exposure in elderly and its response, the overall

6   effect for that study, as you might recall, was

7   .52 percent. In the add-on to SU study, the effect

8   was .6 percent versus placebo, and in that add-on

9   to insulin study, the effect was .54 percent versus

10   placebo.

11   We also have a subgroup of patients in the

12   metformin comparison trial where the hemoglobin

13   A1cs were higher. The number of elderly people are

14   small, but we had about 27 patients in each arm. I

15   just want to show you what happened in those

16   patients with higher A1c with age about 65.

17   Can I have slide 25-11, please?

18   This is the study where we compared

19   metformin and dapagliflozin. This is the treatment

20   effect of dapagliflozin in those patients, age

21   about 65. A point estimate is 1.25 percent

22   lowering. With metformin, it was

1   1.45 -- 1.46 percent lowering.

2   DR. SVANBERG: In addition to these numbers

3   that Dr. Parikh just shared, I would like to ask

4   Dr. Gavin to put this in the treatment perspective

5   of the elderly population.

6   Dr. Gavin?

7   DR. GAVIN: Yes. I deeply appreciate the

8   concern, and it is a real concern because this is a

9   population in whom we expect to see the numbers

10   increase and we expect to see challenges in terms

11   of avoiding those things that make management of

12   diabetes in this population very difficult at this

13   point, not the least of which, of course, is the

14   fear of hypoglycemia in such patients.

15   We would really feel that there would be a

16   significant benefit in having available an agent

17   that could attenuate that risk in this growing

18   population that is compatible with other agents

19   that are currently being used. And clinicians will

20   have the opportunity to use their judgment in terms

21   of assessing ongoing benefit, in making a clinical

22   judgment about whether or not for that individual

1 patient, they're seeing an effect that is

2 sufficient to warrant ongoing use in this kind of

3 population.

4   DR. SAVAGE: The other part of my question

5 was, what if you go to the next older group, say

6 about 75? The numbers, as I read them or tried to

7 get them out of the studies, looked like they drop

8 off pretty precipitously, and there are going to be

9 millions of people in that group.

10   DR. SVANBERG: The program contains

11 approximately 150 patients who are 75 or older. So

12 that is limited information we have.

13   DR. SAVAGE: A fair number of them will have

14 decreased renal function and so forth, so that

15 you'd expect somewhat less effectiveness in that

16 group. The last question I had was, if this drug

17 is used in conjunction with another agent, either

18 insulin or sulfonylurea, any drug that can produce

19 hypoglycemia in older people -- older people are

20 more prone to hypoglycemia when they're treated and

21 they tend to have a poor response, in terms of

22 counter-regulatory response.

1   Does the use of this drug and the,

2   essentially, loss of some glucose in the

3   urine -- have you done any studies to see whether

4   there's any difference in the risk of hypoglycemia

5   or severe hypoglycemia in, again, an older group of

6   people who get this drug plus an active agent that

7   is prone to produce some hypoglycemic episodes?

8   DR. SVANBERG: We have evaluated the safety

9   of dapagliflozin in the elderly patient population,

10   and I will ask Dr. List to address that different

11   evaluation.

12   Dr. List?

13   DR. LIST: When we look at our pool data in

14   the elderly population, and here I'm defining it as

15   greater than or equal to age 65, we see that there

16   is an increased risk of hypoglycemia, both on

17   placebo and on dapagliflozin. So in the greater-

18   than-65 age group, on dapagliflozin, 10 milligrams,

19   there was 13.2 percent of patients who had

20   hypoglycemic events versus, in the under-65 group,

21   it was 9.6 percent. In placebo, over 65, it was

22   9.4 percent and under 65, it was 6.4 percent. So

1   there's an increase in both.

2   When we look into these hypoglycemic events

3   and look at pre-defined categories of major, minor,

4   or other, the major hypoglycemic events were zero

5   in that analysis for the patients greater than or

6   equal to age 65, and it was .1 percent for both

7   dapagliflozin, 10 milligrams, and for placebo in

8   placebo patients under age 65.

9   DR. THOMAS: Dr. Veltri?

10   DR. VELTRI: Yes. Two questions. One

11   relates to renal function, post-therapy. On

12   slide 56, it seemed like there were two -- from the

13   sponsor -- there seemed to be two populations, the

14   overall population, in whom there was a minor

15   diminution in estimated glomerular filtration rate

16   at week 1, but then he returned to baseline and was

17   stable. And in this much smaller population of the

18   moderate impaired renal population, there was a

19   similar drop at one week, but it never really

20   restored back to normal, although it was stable for

21   a little shorter time, one year.

22   So my question is, really, does the sponsor

1   or the FDA have any insights as to why that would

2   be the case between those two populations?

3   DR. SVANBERG: I will ask Dr. Tom Berl to

4   provide the clinical context around the

5   interpretation of this data.

6   Dr. Berl, please?

7   DR. BERL: Thank you. I'm Tom Berl, renal

8   division, University of Colorado. I'm a paid

9   consultant for my input this afternoon.

10   That the decrement of renal function would

11   occur acutely upon exposure to an SGLT2 inhibitor

12   was predicted and seen 70 years ago, when Homer

13   Smith used phlorizin in the history of our field.

14   There is much more noise background in the patients

15   with preserved renal function, and it's my guess

16   that some decrement in renal function is

17   persistent.

18   Now, when we look at decrement in renal

19   function, we wonder whether it's structural or

20   hemodynamic, and there's reason to believe that

21   this is hemodynamic. The slide that you could show

22   here -- what number is it -- 5113, is in a group of

1   patients, 80, 48 of them in whom there was a

2   measurement of estimated glomerular filtration rate

3   when the drug was discontinued. And you will see,

4   in the yellow and green line, at 5 and

5   10 milligrams of dapa, that there was an immediate

6   increment measured seven days later in estimated

7   glomerular filtration rate, strongly suggesting

8   that the observation you made very acutely and

9   perceptively is a hemodynamic event rather than a

10   structural event, which is supported by anatomic

11   studies in experimental animals.

12   DR. THOMAS: I just wanted to know if the

13   FDA wanted to comment on Dr. Veltri's question.

14   DR. IRONY: Yes. I think my other comment

15   is on the second part of your question, which is

16   people with moderate renal failure, that there was

17   a similar magnitude of decrease within the first

18   week, but then there was not recovery to baseline,

19   like you see in people with normal renal function.

20   And we don't know about the outliers of this, and I

21   would ask the applicant about the outliers.

22   The mean suggests that it's a very small

1   decrease, that it would not be clinically

2   significant, of about 4 mls per minute, or 5, or

3   so, in that range, and the mean persists over the

4   course of follow-up.

5   DR. VELTRI: Thank you. My second question

6   relates to bladder cancer again. The sponsor did

7   do one study, which was an add-on study, but it was

8   a small study with pioglitazone. I think it was

9   only a six-month study and maybe only 400 patients

10   in that trial.

11   There was one patient that did develop

12   bladder cancer, I think, at five months. The

13   question I have is, since pio had both a

14   preclinical signal, then pharmacovigilance, what

15   seems to be a real clinical signal, for which the

16   label was adjusted, my question is, from the

17   sponsor or the FDA, since there is a paucity of

18   data and it's unclear, or at least it's uncertain

19   whether it's real or not, for dapa, what is the

20   plan to better elucidate for those patients who are

21   potentially going to be on both of these agents, or

22   will there be some restriction, or how does the

1   sponsor and how does the FDA view that, since the

2   potential for co-administration is there? Albeit

3   with dapa, it may not be real, but certainly

4   there's a numerical imbalance?

5   DR. SVANBERG: There's been sufficient

6   concern raised by several of the speakers here

7   today around the numbers and the epidemiology data.

8   If I could be allowed to please also ask Dr. Brian

9   Strom to first put that in a perspective of

10   epidemiology studies and the databases. And we

11   will thereafter immediately come back to the

12   question around pioglitazone.

13   Dr. Strom, please?

14   DR. THOMAS: I would just ask, because there

15   are some more questions, before you finish, that

16   the comments be brief.

17   DR. STROM: Sure. My name is Brian Strom.

18   I'm chair of the Department of Biostatistics and

19   Epidemiology and vice-dean at the University of

20   Pennsylvania School of Medicine. From a conflict

21   of interest point of view, I'm here today as a paid

22   consultant to the companies. In terms of

1 competitor conflict of interest, I'm also senior

2 author on a study that was recently published that

3 follows up on the association you were talking

4 about, about pioglitazone and bladder cancer. That

5 study, to be clear, uses 30,000 patients in Kaiser,

6 followed for an average of 3.3 years. So we're

7 talking about 100,000 person-years, and we're only

8 midway in the study, along the way.

9   A number of questions have been raised here

10 about comparison -- the signal that's coming from

11 the clinical trial data here about bladder cancer

12 and the comparison, as well, to the SEER data. I

13 think it's important to put that in proper

14 perspective. I think there is a signal hypothesis

15 coming from these clinical trial data. There isn't

16 the pre-marketing animal data mechanistic signal

17 that there was with pioglitazone.

18   So exactly as you stated, whether or not

19 this is real or is random -- because the post hoc

20 analysis of what was not an a priori hypothesis

21 remains to be seen -- adding that to SEER data,

22 comparing it to SEER data, is certainly a common

conventional epidemiological approach, but you have

to be very, very careful in interpreting that.

Firstly, it's still the same exposed

patients. It's not any new patients. It's not

independent. Second, you're comparing apples and

oranges because you're comparing people in a

clinical trial to people in the general population,

especially for a disease like bladder cancer, which

often is not diagnosed for the reasons that have

been discussed before. It's a subclinical disease

until late, at least.

People in a clinical trial are well-known to

be very different, always, to people in the real

world, and people in a clinical trial are likely to

get more intensive monitoring. So you're more

likely to have a detection of early cases of

disease.

So the real signal here is the clinical

trial signal. The SEER data -- the SEER comparison

really adds nothing to that. The way to follow up

on that is to do a study analogous to what we did

in pioglitazone in order to find out whether or not

1   this early clinical trial signal really bears out.

2   I would add that the sponsor in their proposal for

3   post-marketing pharmacoepidemiology studies is

4   proposing exactly that kind of study, but, in fact,

5   many times the size of the study that we have

6   underway for pioglitazone.

7   DR. SVANBERG: Then to the direct question

8   about pioglitazone and dapagliflozin, dapagliflozin

9   and pioglitazone are different in structure, in

10   target, in metabolism, and in data to date. And I

11   will ask Dr. Reilly to present that part of the

12   comparison between the two compounds. And then I

13   would ask Dr. Buse to put the use of dapagliflozin

14   and pioglitazone in a clinical context of a

15   benefit-risk for the patient.

16   DR. THOMAS: Actually, I'm going

17   to -- unless Dr. Veltri, you've got another, I'm

18   going to go onto the next question. Thank you.

19   Dr. Strader?

20   DR. STRADER: I have two questions, one of

21   them on liver disease, about which I know a little,

22   and the other one on oncology, about which I know

1   absolutely nothing. So I'll start that one first.

2   You were talking about the animal studies of

3   bladder cancer. Were there animal studies done in

4   which the bladders of mice or whatever animal you

5   used were exposed to high concentrations of glucose

6   to see if they caused proinflammatory cytokines or

7   some other kind of mechanism that may be

8   responsible for cancer? Because it seems to me,

9   it's a simple issue to determine, whether or not

10   what we're doing in this case, which is increasing

11   the bladder's exposure to glucose, which normally

12   we try to avoid by inhibiting the transporter, if

13   that may be, in some way, responsible for some of

14   the changes or some of the bladder cancers that

15   have occurred.

16   DR. SVANBERG: Yes. The animal studies did

17   induce high levels of glucose into the bladder.

18   And if you wish, Dr. Reilly can provide the data to

19   that point. But glucosuria was seen in the animal

20   studies.

21   Dr. Reilly?

22   DR. REILLY: Yes. As Dr. Svanberg

1   indicated, dapagliflozin is pharmacologically

2   active in both mice and rats. And so we see

3   significant increases in glucosuria in the

4   carcinogenicity studies, upwards of several hundred

5   millimolar, which is several orders of magnitude

6   above normal.

7   DR. STRADER: But did you notice -- did you

8   evaluate the tissue to see if there was any

9   evidence of dysplasia or inflammatory change that

10   might suggest some problems in the future?

11   DR. REILLY: Yes. There were no evidence of

12   any tumors, nor were there any evidence of

13   hyperplastic changes that would be pre-diagnostic

14   for tumors, nor were there any changes that would

15   be inflammatory in nature. Although specific to

16   your question, we didn't specifically look for

17   cytokines, but there was no trigger for any of

18   those risks.

19   DR. STRADER: My second question is with

20   respect to the hepatotoxicity. As a hepatologist,

21   we generally consider patients who are diabetic as

22   having some sort of underlying liver disease, even

1   if they have normal liver enzymes because they have

2   metabolic syndrome; because many of them tend to be

3   obese, they may be on statins, which may cause

4   problems, and most of them have fatty livers.

5   So I was a little bit concerned about the

6   mechanisms for which you try to evaluate the

7   patients who were presumed to have hepatotoxicity

8   and then find it very difficult to make a

9   determination. But I was interested to hear that

10   there was some glucuronidation of the drug in the

11   liver. I'd like to know what percentage of that,

12   of the drug, is glucuronidated in the liver.

13   I'd also like to know, do you know how many

14   of your patients had baseline mild elevations in

15   AST and ALT, and what was that definition?

16   Because, certainly, the definition of normal ALT

17   and AST vary in this country, let alone across the

18   world. And so what was, exactly, the definition of

19   normal AST and ALT?

20   DR. SVANBERG: Dr. Maddrey has evaluated our

21   entire liver data package. I will ask Dr. Maddrey

22   to address that question.

1   DR. MADDREY: I'm Willis Maddrey. I'm a

2 hepatologist from UT Southwestern, and I am a paid

3 consultant for the company. In fact, I've been

4 with this project for some time, actually, becoming

5 involved because of this particular case, the index

6 case.

7   I agree with you entirely. Of course,

8 everyone who looks at diabetic patients finds non-

9 specific elevations. And then on biopsy, in many

10 cases, you find something even more specific, with

11 probably non-alcoholics data, or hepatitis, and its

12 consequences being the most important.

13   I do not know how many of these patients

14 started out with slight elevations. Certainly,

15 most diabetics will be running in the upper half of

16 the normal range for ALT, and the best evidence of

17 that is, after the diabetes gets under good

18 control, in many cases, this falls back towards the

19 lower part of the normal range, a very difficult

20 concept.

21   I would like to just comment just a little

22 bit on the case you're talking about, liver disease

1   here, and this may be the only chance that I get up

2   here. Let me tell you, this is just one case.

3   It's certainly created a lot of angst for me,

4   starting in 2009, and I think that's important

5   because it's the basis of this case, which has been

6   lying around. And I've had an opportunity to look

7   at it just about every month or so since then.

8   As the basis for this case, we set up that

9   adjudication committee, going forward, an

10   adjudication committee. I hope you all realize

11   that when we look at the numbers that were

12   presented by the FDA and by the sponsor, there was

13   no imbalance in the biochemical test, and we have

14   no disagreement. I agree entirely with the FDA's

15   assessment of this. I independently reviewed all

16   these cases, as well as the three members of our

17   panel. And we have one case that we cannot exclude

18   the possibility, rather strong possibility, that

19   it's drug induced.

20   There were a few things, though,

21   interestingly enough about that case. One of the

22   members of the panel, the reviewers, thought very

1   strongly that this had autoimmune overload or an

2   overlaying autoimmune thing. But you've got to be

3   very careful about diagnosing autoimmune hepatitis

4   in a 78-year-old man with no ANA. That's a hard

5   call.

6   I think that, therefore, I had rated this in

7   the probable category, as had two of the members of

8   our panel. But the rest of this, as far as the

9   liver, is in remarkable balance, as far as at all

10   levels, the greater than 3X, the greater than 5,

11   10, and 20. And then the five cases that met

12   Dr. Zimmerman's rule, which we all strongly believe

13   in and many of us have worked with, we only found

14   that one case in that group, and the others were

15   excluded. In fact, the only two cases that the

16   adjudication panel saw rated as probable, as you've

17   already heard, was both of these cases were in the

18   so-called control placebo group.

19   One of the things that gave me a little

20   comfort about this -- and I realize this is swirled

21   around a lot -- is this is a drug given in very

22   small amounts. The idea that drugs that are given

at low amounts, 10 milligrams a day or less, are

less likely to cause hepatic injury has pretty much

stood the test of time. I'd be interested if the

FDA might want to discuss that just a little bit.

But as far as I'm concerned, this one case that we

saw is a case of probable drug-induced liver

disease, but it is only one.

DR. STRADER: Dr. Maddrey, do you know the

number? What's the upper limit of normal for ALT

across the board?

DR. MADDREY: I'd have to ask Dr. List, who

ran the studies.

DR. SVANBERG: We'll ask Dr. List to address

the specific question.

Dr. List?

DR. LIST: As in our clinical program, we

used a central lab. And for that central lab, the

normal range for ALT goes up to 48 units per liter.

DR. STRADER: Okay.

DR. THOMAS: Dr. Felner?

DR. FELNER: Yes. I had a question, I

guess, for either the sponsor or the FDA. I didn't

1	see it, which tells me the answer is probably no,
2	but for the cases of breast cancer and bladder
3	cancer, those individual patients, did you look at
4	the demographics of each one, anything specific
5	that would make them more likely, whether it be
6	history, race, previous mammograms, any of those
7	things? Did you pull them out and look at them
8	individually to see if there was any difference, to
9	make them at least a higher risk for developing
10	cancer?
11	DR. SVANBERG: So I will ask Dr. Dickler to
12	address the clinical picture of the breast cancer
13	patients we saw compared to what clinical practice
14	would be, and Dr. Bajorin to do the same for
15	bladder cancer, please.
16	Dr. Dickler, followed by Dr. Bajorin.
17	DR. THOMAS: I just remind both of the
18	upcoming speakers to be brief and concise.
19	DR. DICKLER: I'm Maureen Dickler. I'm a
20	breast cancer medical oncologist from New York.
21	And if I can show the slide with the patient
22	characteristics. Thank you.

1   So there were nine cases of breast cancer in

2   the dapa group. And as you can see, they really

3   came from various locations and each one from a

4   different country. They were mostly post-

5   menopausal women. And their risk factors varied,

6   but, really, the risk factors among the populations

7   of patients in the clinical trials were well-

8   balanced. And I think that these cancers were very

9   much similar to what an oncologist might see in the

10   general population. They varied with invasive

11   ductal, a few invasive lobular, the majority

12   estrogen-receptor positive. There was really no

13   patient or tumor characteristics that stood out as

14   unusual.

15   Also, I think it's important to note that

16   all of the breast cancer cases were diagnosed

17   within the first year of taking the study drug, and

18   that really is more supportive of preexisting

19   cancer than a causal relationship to the drug, as

20   far as we can tell.

21   DR. FELNER: Was objective if they were

22   appropriate age and had a mammogram prior to

1 entering the study, or any work, anything prior, to

2 be involved in the study, where this could have

3 obviously been picked up before the study?

4 DR. DICKLER: So it's my understanding that

5 a mammography was not specified, but would have

6 been the standard of care within that country, so

7 that these were really detected while on study and

8 we don't have any baseline prior to study

9 information.

10 DR. SVANBERG: Dr. List could address the

11 question and what prompted the diagnosis of these

12 particular questions.

13 Dr. List?

14 DR. LIST: It's just getting to the question

15 of mammography. In following up these cases, we

16 did ask all of the investigators whether there was

17 a prior mammogram. We only got a response from one

18 of them. And in that case, there was a prior

19 mammogram. That patient had been followed up every

20 six months with mammography for a suspicious shadow

21 on the mammogram.

22 With respect to what brought these cases to

1   diagnosis, there were two that were palpated lumps.

2   There were three by mammography. And I'm talking

3   about the cases on dapa. And there were four that

4   we don't have that information, despite asking it.

5   So it takes additional efforts to find out and

6   tease out more and more information. But from the

7   information we have, that's the limits of it.

8   DR. SVANBERG: Then Dr. Bajorin for a

9   similar discussion on bladder cancer?

10   DR. BAJORIN: So could we have the slide

11   34-19, which are the cases with regard to bladder

12   cancer? I think there are a couple observations

13   with regard to this. We talked about hematuria

14   earlier. And hematuria is commonly seen prior to

15   the bladder cancer. And these are the nine cases

16   above the yellow line.

17   The first thing you notice is that several

18   of the cases occurred early, within the first six

19   months. And if you recall from your slide, deck

20   slide 66, two of those patients already had muscle

21   invasive disease, which are actually quite large at

22   presentation.

1   But as you move down, there are several

2   observations. One is, anything that's plus is

3   evidence of hematuria, either trace or above. And

4   if you see an H, H is hematuria reported in the

5   clinical case record of the patient who developed

6   hematuria.

7   So the observation that you see is, 7 out of

8   the 9 patients actually had hematuria very early,

9   either initially on study, or prior to study, or

10 very early on. So this really suggests that these

11 were preexisting diseases.

12   The second observation is that most of these

13 tumors arose very quickly, within 12 to 18 months,

14 which is actually quite short for a carcinogen-

15 induced tumor. If we look at cyclophosphamide, for

16 example, for the most carcinogenic drug that we

17 have, that's in terms of years.

18   Then the third thing I think I'm comforted

19 by with regard to these cases of bladder cancer is

20 there's no preclinical signal that was seen.

21 Virtually all the carcinogens that we're seeing or

22 that we have with bladder cancer, you see

1   hyperplasia as the first evidence. You see that in

2   rodents and dogs, and that wasn't seen in any of

3   the preclinical data.

4   DR. DUNN: I would just like to add that I

5   think there were some patients -- and I don't know

6   if it was just one or more than one -- that had a

7   history of stones. That might have been a cause

8   for the hematuria in some of the patients, or at

9   least one of them, that I recall.

10   DR. SVANBERG: It is correct. One of the

11   patients had an incidental finding of the bladder

12   cancer at the time of stone extraction, and the

13   stone was associated with hematuria.

14   DR. THOMAS: Dr. Seely?

15   DR. SEELY: I had a question in terms of the

16   work you've done on the literature, looking at the

17   families with familial glucosuria. Recognizing

18   that the number is small, of the individuals that

19   can be investigated, I wanted to have a sense of

20   how the degree of glucosuria induced by your drug

21   compares with what you see in the families, and

22   also whether, even in the small numbers, you've

1   been able to see any increased risk of breast or

2   bladder cancer.

3   DR. SVANBERG: The familial renal glucosuria

4   comes in several different mutation settings.

5   There's not one predominant mutation. And

6   depending on the mutation, the degree of glucosuria

7   varies. In the overall literature, these come

8   reported as case reports. We do, from time to

9   time, find that there is an update on the case

10   report -- (indiscernible) 11 years older diagnosis,

11   followed up 20 years later. But they're really

12   dispersed case reports.

13   In communication and conversation with the

14   physicians who come across these patients, they are

15   described as healthy. They are rarely obese.

16   Rather, they have a BMI of 21 or 22. They seem to

17   have a normal lifespan, and it is not known whether

18   they have any bladder or breast or any other

19   cancer. They are described as healthy. But,

20   again, these are scattered case reports, not large

21   cohort studies by any means.

22   DR. SEELY: So the total N worldwide of the

1   patients that actually have the SGLT2 mutation is

2   about what?

3   DR. SVANBERG: The total N?

4   DR. SEELY: Yes. How many subjects

5   worldwide have been described with that mutation,

6   as a cause of the familial glycosuria? Do you have

7   a sense of what that might be?

8   DR. SVANBERG: I do have to recall here.

9   Based on the information that I have, we're talking

10   less than 100 cases, and they do not have the same

11   mutation.

12   DR. THOMAS: Ms. McIntyre?

13   MS. MCINTYRE: I would like to know how did

14   you monitor participants' adherence to recommended

15   dose requirements in the studies.

16   DR. SVANBERG: I will ask Dr. Parikh to

17   address that question.

18   Dr. Parikh?

19   DR. PARIKH: So in most clinical trials, we

20   assessed the use of the drug by looking at the mean

21   and the median doses that the patient took for our

22   study drug, as well as in cases where the

1   background therapy was an essential part off the

2   study. We looked at the mean and median doses of

3   this. And that gave us an idea of what happened,

4   periodically, over the study.

5   DR. THOMAS: We will now take a 10-minute

6   break. Panel members, please remember that there

7   should be no discussion of the meeting topic during

8   the break, amongst yourselves, or with any member

9   of the audience. We will resume at 2:30.

10   (Whereupon, a recess was taken.)

11   DR. THOMAS: We will now begin the panel

12   discussion portion of the meeting. Although this

13   portion is open to public observers, public

14   attendees may not participate, except at the

15   specific request of the panel. We'll start with

16   the first question.

17   The first question is efficacy.

18   Dapagliflozin's efficacy depend on the amount of

19   glucose filtered for the glomeruli. As the

20   glomerular filtration rate declines in renal

21   impairment, the efficacy of the SGLT2 inhibitor is

22   also diminished.

1   Please discuss the implications of the

2   reduced efficacy in type II diabetes mellitus,

3   where renal impairment can impact a sizeable

4   proportion of patients with this disease. Please

5   include in your discussion whether additional

6   studies -- for example, in special

7   populations -- should be conducted to better

8   characterize the efficacy of dapagliflozin in

9   type II diabetes mellitus or whether monitoring for

10   renal function should be performed prior to and/or

11   during treatment with dapagliflozin.

12   We'll start with the comments. If you

13   please raise your hand. Dr. Brittain?

14   DR. BRITTAIN: Hi. Yes. I guess my concern

15   is a bit about the cutoff of 45. It might be the

16   right cutoff, but I haven't seen the data that

17   convinced me that it's the right cutoff. It seems

18   like the safest approach would be to use the data

19   to model the treatment effect as a function of the

20   GFR, and then do another study, and confirm that

21   you really do have the right cutoff, and making

22   sure that the effect looks good really close to

1   that cutoff.

2   DR. THOMAS: Dr. McBryde?

3   DR. MCBRYDE: Thank you. This was one of

4   those areas that I had a lot of issues with. One

5   is, it's unclear, although I think there have been

6   a couple references to using creatinine clearance

7   using the Cockcroft-Gault equation to estimate

8   renal function versus the abbreviated modification

9   of diet and renal disease formula.

10   One of the concerns I have is that the MDRD

11   formula is not a highly accurate formula, that, in

12   fact, at around the stage 3 chronic kidney disease

13   with an estimated GFR of 60 milliliters per minute,

14   per 1.73 meters squared, the variance is about

15   20 percent, which makes me think there's no

16   resolution to split the renal function between 30

17   and 60 in a 15-milliliter per minute increment.

18   The measurement assay is nowhere near sensitive for

19   that, and there are much better assays that would

20   have gotten them much higher precision that could

21   have or should have been done. And so I think

22   splitting it is a very bad idea.

1   Second, I think it also flies in the face of

2   the clinical practice guidelines for the National

3   Kidney Foundation, both for chronic kidney disease

4   as well as for the evaluation for renal disease in

5   diabetics, in which the recommendation in the

6   United States is that the GFR is between 30 and

7   60 milliliters per minute as stage 3 chronic kidney

8   disease.

9   There is some European standards in which

10   the European renal community has recommended

11   dividing stage 3 into stage 3a and 3b, identical to

12   how the sponsor has proposed it. That is not the

13   clinical practice in the United States, and I think

14   it would be quite confusing to practitioners to

15   insert a new definition within the stage 3

16   criteria, based upon a measurement or an estimation

17   of renal function that's imprecise. For the level

18   of this tight narrowing of a cutoff point, I think,

19   is not supported at all by the way that they did

20   it.

21   DR. THOMAS: Dr. Seely?

22   DR. SEELY: So that was why I had asked my

1   question about the effect of GFR earlier. So what

2   I think is that the data supports that the drug is

3   effective for people who are normal renal function

4   or mild renal impairment.

5   Looking at your prespecified goals, it is

6   not effective for lower numbers, although it may

7   be. And I think for even that cutoff of normal

8   into mild, when I asked the question, it was that

9   MDRD was used, but then Cockcroft-Gault was also

10   brought up.

11   So I think we need to know that one formula

12   for eGFR was used across all the populations.

13   Different labs use different formulas for the

14   calculation. If different labs use different

15   formulas in different parts of the world where the

16   studies were taken, it is that you can recalculate

17   and use one standard formula; recalculate the data

18   and then still use your prespecified cut points,

19   but not go back and forth between formula.

20   I think the fact that the data looks like,

21   directionally that in the people with moderate

22   renal impairment, that the ones with less severe

1   moderate renal impairment appeared to have more of

2   a benefit is a positive that then should be pursued

3   in a study that's actually powered to look at that

4   actual population, because that would obviously

5   expand the range of individuals that could benefit

6   from the medication.

7   DR. THOMAS: Dr. Kaul?

8   DR. KAUL: I agree with the previous

9   speakers. I think the data in the 3a category is

10   neither statistically persuasive nor clinically

11   important. And I think, at best, it is hypothesis

12   generating that warrants independent confirmation

13   in a prospective trial. And as such, I think these

14   data are not credible enough to justify a claim.

15   DR. THOMAS: Dr. McBryde?

16   DR. MCBRYDE: I was just going to say, one

17   of the other problems, when I was looking at it, I

18   think -- I certainly, I have to admit, have a

19   little bit of envy seeing Dr. Berl stand up and

20   present. And that slide, what was interesting to

21   me was that it said that it was estimated GFR,

22   which would presume that it was used using the MDRD

formula. The problem is, the MDRD formula has ever

only been validated in patients with stage 3 or

worse chronic kidney disease. So you can't publish

an eGFR of 78 milliliters a minute because MDRD has

no validity above 60. Above 60 milliliters a

minute, you can only report the eGFR as greater

than 60 milliliters a minute. You cannot be that

precise.

It was something that I've seen in the

published literature of dapa as well, is that the

authors are reporting eGFRs of 90 milliliters a

minute. With MDRD, you can't. There's no validity

to making that statement. It's meaningless. So if

you're going to use MDRD, the only criteria you can

really say is, greater than 60, less than 60,

and/or less than 30, or less than 15, as the stages

of chronic kidney disease get worse.

The other thing that strikes me is I'm a

little disappointed that, given the high protein

binding -- 91 percent of this drug is highly

protein bound -- the free fraction is filtered at

the glomerulus. And like many drugs, although not

1   directly stated, I would presume that the free drug

2   has to bind the SGLT2 receptor in the brush border

3   in the S1/S2 segments of the nephron.

4   Proteinuria, terribly common in diabetics

5   and usually often one of our first signs of chronic

6   kidney disease, has not been evaluated by the

7   sponsor. What's the impact of albuminuria, normal

8   albuminuria, macroalbuminuria over proteinuria? We

9   don't know what that impact would be. My suspicion

10   is that with intertubular or intraluminal binding

11   of the free-filtered fraction to urinary proteins,

12   the drug's not going to have much of an effect.

13   DR. THOMAS: If there are no further

14   comments, I'm just going to add one, which is,

15   eGFR, in addition, I don't believe has been

16   validated in many different racial groups. And so

17   we may not be able to use that criteria in many of

18   the groups that may actually use the medication or

19   drug if it's approved.

20   If there are no further comments, I'll

21   summarize the discussion that we had for

22   Question 1. First, there was concern of different

1   committee members on the cutoff of eGFR 45. One

2   possibility is that this is not a valid use of

3   eGFR. Once it's above 60, there's no real

4   discriminatory ability, and once it's below 60, the

5   discriminatory ability occurs at 30. And

6   arbitrarily dividing it into 45 to 60 versus 30 to

7   45 may not be an appropriate use of this

8   measurement.

9   It would be important to consider,

10   prospectively, additional studies to assess the

11   creatinine clearance for glomerular filtration rate

12   and potentially use other methods of estimation of

13   this that may be more accurate than an estimated

14   GFR formula. Statistically, based on the data that

15   was presented by the sponsor, it does not appear

16   that there is efficacy below than 60 unless

17   additional data from a trial, prospectively, is

18   performed.

19   Furthermore, there was concern about the

20   classification of 3a and 3b for kidney disease. In

21   the United States, that classification does not

22   exist, where it may exist in Europe. And this

1   might add confusion to practitioners if this

2   medication was approved in the United States,

3   having those criteria separate into 3a and 3b.

4   Finally, there are two points that need to

5   be made. One is that there are multiple ways of

6   estimating creatinine clearance or eGFR. And

7   depending on where these studies were done, they

8   might have used a different one for entry into the

9   trial. It would be best if the sponsor could go

10   back and analyze the data using one consistent form

11   of criteria. That way, it would be easy to assess,

12   clinically, for a person who might be prescribed

13   this medication, is the patient an appropriate

14   candidate for this drug. If you use different

15   criteria, then it would be more confusing as to

16   which test to use to determine if efficacy is

17   possible.

18   Then finally, there is this question about

19   micro- or macroalbuminuria and proteinuria.

20   Because the medication or drug is protein bound,

21   there could be impact at its effect on the SGLT2

22   site in the kidney and the S1/S2 segment of the

1   tubule. And as a result, there does need to be

2   studies of populations with micro or

3   macroalbuminuria to see if the efficacy is

4   diminished because of the effect of protein in the

5   lumen.

6   We'll now go onto the second question, which

7   is about hepatic safety.

8   Dr. Veltri, do you have something to add?

9   DR. VELTRI: Yes. I just have a question.

10   It sound like one of the important parts of this

11   question was whether monitoring should be performed

12   during treatment as well, since diabetes is a

13   progressive disease, potentially affecting the

14   kidney. So I think that's an important question.

15   Maybe the FDA, certainly, and sponsor, would like

16   to know what the panel's opinions are on that.

17   DR. THOMAS: That's a good point.

18   DR. IRONY: Yes. That's a good point that

19   Dr. Veltri raised, and it's an important component

20   of Question 1, is even in patients with normal

21   renal function, mild renal impairment, what happens

22   when the disease progresses and you see that people

1   have a decrease in GFR, and how would we handle

2   this in a patient taking an SGLT2 inhibitor?

3   DR. THOMAS: So would anyone want to comment

4   on monitoring that's required for this agent?

5   Dr. McBryde?

6   DR. MCBRYDE: I'll try to take a crack at

7   this. I think if you screen the patient, the

8   diabetic patient, with a serum creatinine, and your

9   lab is one of the nice ones that gives you an

10   estimated GFR, and you receive an estimated GFR of

11   greater than 60 milliliters per minute per

12   1.73 meters squared, in the absence of

13   albuminuria -- and here's the difficult part. I

14   don't know where that cutoff would be because of

15   the absence of data on that.

16   So I guess the conservative approach would

17   be to say that if you have microalbuminuria,

18   between 30 and 300 micrograms per milligram of

19   creatinine, or overt proteinuria with an albumin to

20   creatinine ratio of greater than 300, that, in

21   fact, you probably shouldn't be taking this drug,

22   mainly because we don't have any evidence that

1   there's any efficacy in that particular population.

2   That would be the most conservative.

3   Basically, normal albuminuric, eGFR greater

4   than 60, okay to use the drug. If you develop

5   albuminuria on the drug or you start to see eGFR

6   drop below 60, I think that should be the stop

7   sign, at least in the present absence of other data

8   provided by the sponsor to support that it's still

9   safe to use the drug, safe and efficacious.

10   DR. THOMAS: Dr. Seely?

11   DR. SEELY: I was just going to make a

12   comment in terms of frequency of monitoring once a

13   patient was on the drug, is to try to make

14   recommendations that might be compatible with other

15   diabetes recommendations. And to say that, at the

16   time of a urine check yearly for microalbuminuria,

17   if an eGFR has not been calculated within the past

18   six months to check it, at a minimum of yearly.

19   DR. THOMAS: I was just going to say, I

20   think that's an important point, that unlike many

21   medications, where we start that, and just start

22   them, and just continue them, as efficacy wanes,

1   really, this is an unusual class of drugs where

2   efficacy does go down with renal function as it

3   changes. And as a result, we would have to have

4   consistent monitoring to make sure the efficacy is

5   still there, rather than just adding on additional

6   agents when efficacy is diminished.

7   I can briefly summarize this, if there's no

8   further comment.

9   Dr. Capuzzi?

10   DR. CAPUZZI: Just one point. In some

11 situations, it may even be necessary to do a

12 creatinine clearance in a specific patient to get

13 some idea, instead of using an estimated one, but

14 that's just my opinion.

15   DR. THOMAS: So to summarize the question

16 that was brought up about monitoring or testing

17 involved for this medication, the most conservative

18 method would be to get an estimated GFR or some

19 other appropriate measure of creatinine clearance,

20 and if there's no presence of micro or

21 macroalbuminuria, to use the medication. That

22 would be the most conservative approach, as we

don't know actually what the effect of protein in

the urine has on the efficacy of this medication.

In addition, some people may require

creatinine clearance. And, furthermore, to not

burden the patient with having to have more

frequent testing, if possible, in a realistic

strategy, it would be best to try and combine

testing annually with what is normally done for a

patient with diabetes, such as testing urine

microalbumin, which is usually done yearly.

We'll now go onto the second question, which

is about hepatic safety. Five patients treated

with dapagliflozin developed ALT or AST greater

than three times the upper limit of normal, with an

accompanying total bilirubin of two times the upper

limit of normal, biochemical Hy's law.

An adequate explanation for the biochemical

abnormalities could be identified in all but one

case. This one case was classified as a probable

diagnosis of mild to moderately severe

dapagliflozin-induced liver injury.

Imbalances in severe hepatic transaminase

1   elevations greater than 5 to 10 times the upper

2   limit of normal, between dapagliflozin and

3   comparators, were not observed and no signal for

4   hepatotoxicity was identified in the non-clinical

5   program.

6   Please comment on the clinical relevance of

7   the one case and whether sufficient evaluation has

8   been conducted pre-marketing to determine if

9   dapagliflozin is associated with the risk of

10   hepatotoxicity.

11   Dr. Strader?

12   DR. STRADER: I have been asking this

13   question a couple of times at this meeting. I

14   think that it's important in patients who have

15   underlying liver disease, such as diabetics who may

16   have metabolic syndrome, or fatty liver, or

17   alcoholics who may have underlying liver disease,

18   that if they are being involved in studies of new

19   drugs, and all drugs have some potential of

20   hepatotoxicity, that there is some sort of protocol

21   by which these patients are evaluated.

22   It's my opinion that it's always a good idea

1 to know before the patient is started on the study

2 what the pattern of liver enzymes have been, and

3 then once they're started to have frequent

4 monitoring, the same way we talk about it for renal

5 disease, because with drug-induced liver disease,

6 it's extremely difficult to determine a causal

7 relationship. And so you need to have values at

8 pre-determined time points so that you can evaluate

9 exactly what's happening when.

10 In addition, it's important, because of all

11 the other concomitant medications, to have some

12 sort of idea of which ones may also be hepatotoxic,

13 whether the patients are encouraged or discouraged

14 from using unnecessarily medications; that kind of

15 thing, is very important.

16 I've found it difficult, looking at the

17 cases that were presented here, to make a strong

18 determination because the time points at which I

19 had results varied from case to case, and some

20 patients had baseline mild abnormalities; others

21 did not. And so it was a little bit difficult. So

22 I think the issue of monitoring and evaluating

1   patients pre-study, and during the study, and

2   particularly when something happens, is extremely

3   important.

4   DR. THOMAS: Dr. Avigan?

5   DR. AVIGAN: I just wanted to add one point

6   that did come up in our discussions, which is the

7   imbalance question. And, of course, different

8   drugs that have, over time, declared themselves as

9   being potentially hepatotoxic, idiosyncratic in

10   some patients, have had, historically in clinical

11   trial development, different levels of imbalance.

12   So in some cases, they're extraordinarily large

13   imbalances, but in other cases, they have not.

14   One of the things that was mentioned by

15   Dr. Maddrey is to look at the comparator group for

16   potential other reasons why there may be elevations

17   in the comparator group for percentages of ALT

18   rises in that group. And in patients with

19   diabetes, there's a high background rate of NASH.

20   It's notable that, in the diabetes prevention trial

21   at the NIH, which was, again, a diabetic population

22   along the way, there was a high rate of ALT rises

1   in the comparator groups not on troglitazone. So

2   there are different scenarios where that level of

3   imbalance as one of the signals for hepatotoxicity

4   potential may be lessened.

5   The other point I do want to make is that in

6   our review, Dr. Seeff felt very strongly that the

7   autoimmune diagnosis was not a tenable diagnosis.

8   DR. THOMAS: Dr. Spruill?

9   DR. SPRUILL: I was going to comment on the

10   clinical relevance of this case. I think this case

11   referenced an American Indian. Am I correct? Yes?

12   DR. THOMAS: I think it was someone from

13   India, but the sponsor could correct me if I'm

14   wrong?

15   DR. SPRUILL: Was it East India?

16   DR. SVANBERG: The patient is from India,

17   living in the United Kingdom.

18   DR. SPRUILL: I got you. Okay. The point I

19   was going to make, though, was that I think

20   patients respond to drugs differently and

21   metabolize drugs differently because of genetic

22   makeup. And I want to go back to my point I said

1 earlier. I think the clinical relevance of this is

2 that I think it's important that people who are

3 overburdened by diabetes should be represented in

4 these clinical trials.

5   DR. THOMAS: Ms. McIntyre?

6   MS. MCINTYRE: I think the mere fact that

7 this case came about is a flag that this is a case

8 that needs to be -- unfortunately, it wasn't

9 further investigated because the patient withdrew.

10 But it does let us know that the possibility does

11 exist. And so it needs to be further evaluated.

12   DR. THOMAS: Just to add to this, does

13 anyone want to comment on any type of testing or

14 monitoring that should be performed?

15   DR. STRADER: I noticed, FDA, that you do

16 have guidelines for evaluation of drug-induced

17 liver injury, but they are not mandates; they are

18 suggestions. It's not binding. And so that makes

19 it a little bit difficult when you're trying to

20 evaluate cases which are extremely difficult to

21 establish a causal relationship if you have

22 guidelines that aren't binding. So you don't have

1   to check every two weeks if you don't want to, but

2   we suggest that you should.

3   I think it may be an important thing to make

4   those a little bit more stringent, so that if there

5   is a case in which there is suspected

6   hepatotoxicity, that we're doing exactly what we're

7   supposed to be doing in the correct order so that

8   we can properly evaluate the cases when they come,

9   as opposed to having data points that may not

10   necessarily be helpful.

11   DR. THOMAS: Dr. Capuzzi?

12   DR. CAPUZZI: Just a very minor point. I

13   agree with everything that was stated. I think

14   it's always useful, even though this is not a real

15   sensitive test, to get a serum albumin level. I

16   mean, if it's four or five and the transaminases

17   are borderline, albumin. maybe even a pre-albumin,

18   but certainly an albumin. And I think that would

19   help, too.

20   DR. THOMAS: Just to make sure, before I

21   conclude this question, any other discussion on the

22   necessity for additional pre-marketing testing or

1   pre-approval testing?

2   [No response.]

3   DR. THOMAS: I thought I'd have one quick

4   question for the FDA for comment. So the data

5   would seem that this is balanced, but the one case

6   is the concern, just to make sure that everyone's

7   clear.

8   DR. AVIGAN: I just want to comment on what

9   we mean by liver signal, because this is a very

10   important point. The idea that a Hy's case

11   is -- when we talk about a Hy's case, what we mean,

12   my understanding, is that this is a liver injury

13   event, which is probabilistically associated with

14   the test drug.

15   So we've gone through identifying a case

16   with acute liver injury, hepatocellular injury, and

17   we've done differential diagnosis to exclude other

18   causes. But because there are potentially small

19   residue uncertainties, we give a probabilistic

20   analysis of where we think the causal link is.

21   In this case, it was called by the

22   adjudicator at the FDA, probable, which means that

it's a probably linked case to the drug, the test

drug. If that's true, and if we knew for sure

that's true, then we know that this drug, at least

in that individual, who is susceptible, had the

potential to cause hepatotoxicity, and then

projecting to a large exposure population would

then assume that there are other people in the

population who may have similar susceptibilities.

This is not a measure of prognosis. This is a

measure of risk in an exposure population.

So that's the key concept. So when we argue

about or debate causality, why we say one case is

worrisome, two are quite concerning, is, once we

have two, each probabilistically linked, we know

the drug is linked to this potential.

So this is what this discussion has been

about and there's, I think, from the discussion and

from the reviews, some concern with this drug

because of the causal link in this particular

patient. But it's only one case where we could

determine that, and that's what we're left with at

this point in time.

1   DR. THOMAS: Dr. Veltri?

2   DR. VELTRI: I would just like to ask the

3 FDA, and it may help with the sponsors as well,

4 it's a probabilistic assessment. What if it was

5 definitive? What if it was definite? Would that,

6 in any way, shape, or form, color your approach to

7 this? Because probable means yeah, perhaps, but

8 maybe not, as opposed to definitive, it's pretty

9 clear cut.

10   DR. AVIGAN: So once you knew that it was

11 definitive, if you had that information, then you

12 could say that, based upon the denominator of

13 exposure in the test population, you could begin to

14 project, if you assume the equal distribution of

15 risk and its susceptibility across the treatment

16 population, a number or incidence rate that you

17 might expect once you put it out there.

18   Now, the problem with -- even if it's true

19 in one case and we do these extrapolate projections

20 of 10 percent having serious and so on, it's a very

21 unstable number. So if you apply any sort of

22 statistical magic to this, the confidence intervals

1   around that point estimate are going to still be

2   very wide.

3   So historically, in the end, with

4   hepatotoxins, drugs that turn out to have this

5   idiosyncratic hepatotoxicity potential, the real

6   risk, incidence risk, really declares itself over

7   time with multiple data sources of information.

8   But the first question in the algorithm is, can it

9   cause this event, and that's what I think we're

10   discussing today.

11   DR. THOMAS: Dr. Smith?

12   DR. SMITH: Yes. That's all well and good.

13   And I think that those of us who don't think about

14   these clinical trials every day certainly benefit

15   from hearing the theoretical underpinnings of a

16   thoughtful discussion. But I think that, now, we

17   have to move on to the practicality of, so we've

18   got this one case, and how is this going to impact,

19   or should it impact the deliberations going

20   forward, in terms of recommending stringency of

21   monitoring, frequency, scope of monitoring, and all

22   with the idea of mitigating whatever risk there is

1   that's been uncovered?

2   DR. AVIGAN: I'll just make one final

3   comment. So there are two kinds of questions with

4   regards to monitoring. In a clinical trial, we

5   monitor to protect patients, and also because we

6   have them systematically available to us, but also

7   to learn when they have these events.

8   In a general post-marketing population, we

9   monitor because it has an impact on mitigating

10   risk. Now, the issue here is that these are, at

11   best, very rare events, if they occur at all. So

12   our general experience with post-marketing

13   monitoring is that it generally has not shown

14   itself in any case in particular to be a useful

15   strategy for drugs that cause these events rarely.

16   So I would distinguish monitoring practices

17   in clinical trials from which we are learning about

18   the patient and the risk, but also protecting test

19   subjects from what we do in clinical practice.

20   DR. SEEFF: I would like to make a comment

21   about the causality as to drug-induced liver

22   injury. I guess everybody knows here that there is

1 no biomarker that gives us --

2   DR. THOMAS: Would you be able to identify

3 yourself?

4   DR. SEEFF: I'm Leonard Seeff. I'm a

5 consultant in hepatology to the FDA. I speak with

6 a background of having spent 10 years at the NIH,

7 working on the drug-induced liver injury network

8 study, in which one of the focuses was trying to

9 come up with a causality assessment of

10 hepatotoxicity and severity. So there was a

11 background to this information.

12   There is no way of making a definitive

13 diagnosis in drug-induced liver injury. All you

14 can do is to deal with the fact that you exclude

15 every other known cause. Once you have a potential

16 relationship between the receipt of a drug and the

17 development of a liver dysfunction, once you've

18 come up with that, you have to grade it. And the

19 grading severity that the NIH came up with was the

20 one we're talking about here on definite, which was

21 more than 95 percent likely, highly likely, which

22 was 75 to 94 percent, probable, which is 51 to 74

1   percent, and so on, and so forth.

2   We struggle with this all the time, and I

3   can tell you that we review cases, and we have

4   three or four reviewers, and we don't always agree.

5   My own belief is that I would never call a case

6   definite, which is a new case, a new drug. We

7   don't have enough information. In order to come up

8   with a definite, you need to have a history. Has

9   this drug been used before? Has it caused liver

10   injury? What is the latency between the use of the

11   drug and the development of the abnormality, et

12   cetera, et cetera? You take into account all of

13   these factors.

14   So when I called it probable, I would never

15   have personally considered this definite. This is

16   a new product. I have no history of what this

17   might do. So it's a question between probable and

18   highly likely.

19   My own view is that in the 78-year-old man

20   who's serum negative for autoimmune hepatitis, I

21   guess that the view that this could be autoimmune

22   hepatitis came from the pathologist, who said that

there was piecemeal necrosis, which was what you

see in autoimmune hepatitis. But it's not specific

for autoimmune hepatitis. You can see that in

drugs, and there are drugs that lead to autoimmune

hepatitis, nitrofurantoin, minocycline. You cannot

distinguish. It's very, very difficult.

So making the diagnosis is very difficult.

I believe strongly that this is as good a case as

one could get for a diagnosis of drug-induced liver

injury. Now, there are other drugs that were seen.

We have to work out which was the best. So I think

that it's a very difficult problem.

I would also like to make a comment about

this issue of imbalance. The view that is taken is

that there's no imbalance, there is no drug

hepatotoxicity. But what we don't know is, what

was the cause for the abnormalities in each of

these cells? Were they the same?

I think that you have to evaluate.

Dr. Strader's absolutely right. You have to

evaluate every case. And not only do you say that

this is not drug-induced liver injury, but what is

1   it? It is extremely important, I think, to do

2   that, so that any drug that is being evaluated

3   should be carefully monitored. You should find the

4   abnormality, set whatever standard you wish for

5   saying this is an abnormality that's of concern.

6   Maybe you need two values above, three times, or

7   whatever it is, the upper limit of normal. But you

8   evaluate the cause. That's extremely important.

9   Dr. Senior, who's one of the experts in

10   drug-induced liver injury, makes this point all the

11   time. It's not a question of saying either it is

12   or is not drug-induced liver injury; it is, what is

13   the cause for the abnormality? And I think that

14   saying that there's no imbalance is useful, but it

15   is not definitive. You have to say, I know that

16   the reasons for the fact that there is no imbalance

17   is because they have the same reason. But if you

18   find a serious liver case in the one and not in the

19   other, that's a different story.

20   So that's my sense of this issue of how to

21   make a diagnosis. It's extremely difficult. We

22   all struggle with this. But I think we're getting

1   better as we go on.

2   DR. THOMAS: Thank you. I don't see any

3   additional comments, but before I summarize, I was

4   going to ask the FDA if they thought there was

5   sufficient discussion on this question or if we

6   need to try and answer your questions.

7   DR. IRONY: I just want to have a little

8   clarification from Dr. Strader. You mentioned

9   about the guidance, the FDA guidance not being

10   mandatory. And what we have in clinical trial

11   protocols is some plan about how we are going to

12   enroll that kind of population that has a

13   transferase that's less than three times the upper

14   limit of normal or less than two times the upper

15   limit of normal.

16   We are going to follow them at periodic

17   intervals, just like we follow for renal safety, or

18   CBCs, or et cetera. And if there are some

19   abnormalities, we're going to investigate further

20   and discontinue the study drug in case there is

21   some elevation above a certain prespecified

22   threshold.

But the protocols don't mandate what exactly the adequate workup would be and that's left to the individual investigators. Similarly, the guidance only makes recommendations. You need to test for viral hepatitis. You need to test for EBV or CMV in certain particular populations that are at high risk for those and for other reasons. But we don't mandate the particular workup because we realize this imposes on the practice of medicine.

DR. THOMAS: Yes, Dr. Strader?

DR. STRADER: Yes. This is a difficult issue, as Dr. Seeff mentioned. I think that when applicants come with new drug applications, there needs to be some sort of leeway in how they evaluate things. But the problem is, with a case like this, once there is the suspicion that there is drug-induced liver injury, I think that the nebulousness with which we evaluate the patient should disappear. There should be very strict methods of when you evaluate the next liver enzyme abnormality and what you do if it's still going up; when do you stop? When do I get a liver biopsy?

1   When do I do an ultrasound? When do I do a CT

2   scan, this kind of thing, as opposed to saying,

3   well, on day 50, he had this, and then we waited

4   until day 100, and he still had it, and so then we

5   did this. Because it becomes very difficult to

6   make any kind of determination, when so much time

7   has passed in between and there hasn't been any

8   sort of evaluation that is in a regimented manner.

9   Now, having said that, I don't know exactly

10   what that should be. But certainly, you all have

11   had some guidance, and so you've given this some

12   thought. And so perhaps making it a little bit

13   less nebulous and a little bit more binding might

14   be helpful in being able to determine, in the

15   future, what the causality is.

16   DR. THOMAS: So I'm going to summarize the

17   discussion for Question 2. Even though there is

18   balance in the ALT, and AST, and other enzyme

19   abnormalities, there is great concern because there

20   is one isolated case, which is a probable

21   designation of being related to the drug for liver

22   toxicity. It seemed unlikely that this would be

1 autoimmune hepatitis.

2   One of the problems of studying patients

3 with diabetes in general, who also have obesity, is

4 that they may have an underlying disease pattern of

5 enzymes before or after the initiation of the

6 medications. Many of these patients may have a

7 high rate of NASH before they entered the study.

8 There are also other medications they take,

9 including classes such as statins, that could cloud

10 the picture of what's the cause of the liver

11 injury, or liver function, or even potentially

12 interact with another agent to cause this.

13   This one case, clearly, is a red flag, and

14 there was also concern that there are differences

15 in different racial or ethnic groups because of

16 maybe, potentially, genetics or metabolism that

17 can't be really addressed because of the numbers of

18 subjects of other racial groups that were in this

19 clinical trial protocol.

20   We definitely would need more stringent

21 evaluation of the liver disease or changes in

22 transaminases in any studies that are performed to

1   evaluate this further; for example, more frequent

2   testing. And where currently it is left up to the

3   investigator as to what's the course of evaluation

4   after a liver injury is identified, probably there

5   should be strict specification of diagnostic

6   testing, follow-up, and timing for any identified

7   cases in any future pre-marketing study.

8   That'll be the end of that question.

9   Now, we'll go onto Question 3, which is

10   about breast and bladder cancer. Numeric

11   imbalances in breast and bladder cancer observed in

12   the clinical development program. For both of

13   these types of cancer, please discuss whether these

14   imbalances signify a risk for carcinogenic

15   potential associated with dapagliflozin.

16   In addition, please comment on whether the

17   numeric imbalances are impacted by the following:

18   any imbalance of baseline risk factors, any

19   detection bias.

20   Dr. Piantadosi?

21   DR. PIANTADOSI: Thank you. I have several

22   paragraphs of comments on this question.

1   Is it okay to read them into the record?

2   DR. THOMAS: I think so.

3   DR. PIANTADOSI: So I'll comment

specifically on the evidence for cancer risk,

particularly that for breast and bladder cancer.

There is uncertainty in the data, as we're all

aware, but my view is that there's not a lot of

uncertainty on how to evaluate the evidence or,

ultimately, on the best course of action.

          I don't want my colleagues to conclude, for

example, that uncertainty implies no evidence of

harm, or to conclude that evidence of risk must

turn us away from a potential useful tool. What I

hope is that we all face the facts as they exist

today, make an appropriate decision, and obtain

additional data if we agree that it is required to

inform future actions.

          The view of cancer risk that I'll outline is

consistent with there already being safe and

effective therapies for this condition available,

and that this is a serious disease, but compatible

with substantial life expectancy. The FDA and

1   sponsor have agreed on the appropriate treatment

2   and control groups for these analyses, as well as

3   the number of cancer cases in the comparison

4   groups.

5   The appropriate comparator group for safety

6   is, apart from small differences, the same as that

7   for efficacy. One cannot sensibly believe in

8   efficacy conclusion and disbelieve a safety signal

9   coming from the same data. To that point, the

10 reference to SEER data is sensible, and

11 interesting, and well done, but is fundamentally a

12 misdirection.

13 The cancer relative risk is directly

14 estimable from the efficacy comparison groups with

15 the cautions I mention below. For these reasons, I

16 will emphasize only the risk estimates that derive

17 from the same source as the efficacy estimates. If

18 a new study were to be planned, the SEER estimates

19 are key for helping to determine its size.

20 The data suggest cancer risks for breast and

21 bladder cancer in the four- to fivefold range.

22 Such risk ratios are always biologically

1   significant and may be clinically significant,

2   depending on the baseline risk and the size of the

3   population at risk. Statistical significance is an

4   important question, and it reflects on the validity

5   of the possible risks. But lack of statistical

6   significance does not make the relative risk zero.

7   It merely creates uncertainty regarding the most

8   reliable inference from the data.

9   If the cancer risks were statistically

10   significant, I don't think we would be here today.

11   Mitigating the putative cancer risks are the

12   following. There's no clear mechanism for

13   carcinogenesis. There's no evidence of

14   mutagenicity or carcinogenicity from preclinical

15   studies. Some effect might be attributable to

16   detection bias. However, the relative risks may be

17   too high to be fully explained by such, and some

18   cases were probably prevalent.

19   The sponsor chose to emphasize the cancer

20   risks in terms of the incident rate difference,

21   which is relevant, but may not be as important to

22   the individual patient as the more common and I

1   believe more relevant risk ratio. When the control

2   counts were zero, use of the incident rate

3   difference was sensible, and I'll say more about

4   that below.

5   With regard to the worrisome aspects of the

6   cancer risk, the baseline imbalances are not likely

7   to explain the cancer findings. There can never be

8   any surrogate for safety. The evidence must come

9   from direct exposure and ascertainment.

10   Cancers are mechanistically complex and one

11   cancer type or its absence is not a surrogate for

12   any other. Even removing some of the prevalent

13   cases, we are likely left with relative risk

14   estimates greater than 2, for example.

15   The breast and bladder cancer findings could

16   be due to chance. We all know this and might

17   wishfully think that it's the right explanation,

18   based on mechanistic arguments. However, the

19   purpose of a rigorous valid comparative study

20   design -- and this one is admittedly

21   imperfect -- is to free us from the uncertainties

22   of mechanistic argument and allow us to draw

conclusions from empirical data. When properly

done, such evidence trumps all and teaches us to

look for mechanisms or not.

In short, empirical evidence is the equal

and necessary partner for mechanistic biological

reasoning. The paradox of invoking chance as the

sole explanation for the observed events is that we

might then also have to admit that chance has

caused us to miss other safety signals.

I would be willing to admit that some of the

apparent adverse effect of the drug can be

attributable to ascertainment bias in the dapa

group. How much of the multifold risk of breast

and bladder cancer to discount by such reasoning is

not obvious, and I personally am not willing to

disregard 100 percent of it any more than I'm

willing to discount the apparent treatment effects.

The FDA-updated data, agreed to by the

sponsor, unfortunately for the drug, removes the

statistical uncertainty of zero denominators and

permits estimated risk ratios of 5 for bladder

cancer and 4 for breast cancer, both non-

significant at the conventional 05 level, but very worrisome.

It was said this morning that there are 26 million Americans with diabetes. Let's assume for a moment that 10 percent of them will use this drug. If the true cancer rates are then about 0.3 percent, as the data suggest, this translates roughly into 7500 bladder cancer cases, 6,000 of which are excess, and 3500 female breast cancer cases, 2500 of which are excess. There might also be 25 cases of both malignancies, essentially all in excess, that could be attributed to the drug. If only 1 percent of patients use this drug, there is still a significant burden possible if the cancer risks are accurate.

These are my guesses for illustration, based on short-term exposure as in the current databases. Long-term exposure could be associated with higher event rates. Also, some patients contributing to these rough estimates receive only one-quarter to one-half of the dose as others.

Effects of this magnitude are not ignorable

1   or precautionary, and as I hinted above, would have

2   the same pedigree for validity as the hemoglobin

3   A1c treatment effects, apart from the greater

4   precision with which the latter is estimated.

5   Although the trials were not designed to estimate

6   these or any rare event with high precision, they

7   do permit detection of a possible signal.

8   Unfortunately, there is a cancer safety

9   signal in the data that we cannot reasonably pare

10   down to zero without more information. We must

11   recognize the strengths and weaknesses of the

12   evidence in support of the signal and draw

13   conclusions in light of it.

14   What are the right conclusions?

15   Unfortunately, neither a biological mode nor a

16   statistical mode of reasoning will alleviate the

17   dilemma. A definitive risk assessment remains

18   impossible presently. I would leave the final

19   risk-benefit assessments to topical experts, but I

20   am impressed by the magnitude and scope of the

21   problem, as well as the basic efficacy of the drug.

22   I encourage the FDA to respect the data, as

1   well as places where the data may be thin. My

2   advice is not to ignore cancer-relative risks that

3   might be as high as four- to fivefold. As an easy

4   example, it seems to me there is little

5   justification for use of this drug in moderate to

6   severe renal impairment, especially given the

7   safety concerns. If I were taking this drug, I

8   would want to know that I might be exposed to this

9   significant a relative risk for bladder cancer.

10   If the drug is approved for marketing, I

11   would want to see a large additional study whose

12   design specifically permits the assessment of the

13   index cancers. The study should have active

14   ascertainment of cancers. It would be best if such

15   a trial were randomized. As I indicated in my

16   earlier comment, it would free us almost completely

17   from biological rationalizations.

18   I would be most pleased if more well-

19   designed data showed cancer risk to be negligible.

20   It would also be acceptable to know, with adequate

21   precision, if the risks are higher. What would be

22   unacceptable is to expose large numbers of diabetic

1   patients to a serious, preventable risk that

2   defines itself late. Thank you.

3   DR. THOMAS: Anyone else have a comment?

4   Dr. Seely?

5   DR. SEELY: I think the sponsor was very

6   honest that they could not find an imbalance in

7   baseline risk factors. I thought the issue that

8   there be a detection bias is one that needs to be

9   explored more. So we know mammography is very

10   difficult in obese individuals, and the American

11   Society of Radiologists puts out special

12   recommendations for how to do mammography in obese

13   individuals. And if obesity decreases and there's

14   fat loss in the breast, the mammogram becomes

15   easier to perform and more exact.

16   So I think we have, at least for the breast,

17   a good reason why, if there is associated weight

18   loss, it would unmask lesions that may not have

19   been detected until later. And early detection may

20   actually be of benefit in this population.

21   So what we may be doing is finding it

22   earlier in these women who, in two to three years

1   without the weight loss, may have been diagnosed

2   with a later breast cancer. The other is that

3   hydration status may affect breast imaging. And if

4   there is a direct effect, that may affect the

5   imaging as well.

6   So it might be worth trying to look more

7   directly at the amount of weight loss seen in some

8   of the individuals, and to actually get some of the

9   mammograms that have been done on your population

10   that were in the beginning and the end, and look at

11   changes in mammographic density, according to what

12   treatment arm they were in, because over time, the

13   density should be decreasing, just with aging. But

14   you may find some increasing in your treatment

15   population because you're losing fat and that may

16   give some of the answer to the discrepancy.

17   DR. THOMAS: Dr. Strader?

18   DR. STRADER: Can I ask you a question on

19   that point? Do you know how much weight one would

20   have to lose in order for it to be impactful?

21   Because I think the applicant said that there was

22   maybe a 3 and a half kilogram loss over a six-month

1 period of time. So that doesn't sound like a lot

2 of weight. And most of the breast cancers were

3 diagnosed within a year of starting the drug, so

4 that doesn't give you a whole lot of time.

5   DR. SEELY: That's why I thought it would be

6 helpful to look in those specific cases, because

7 the mean was around that amount of weight. But the

8 weight loss may have been more dramatic in the

9 women who developed breast cancer. And obviously

10 what's hard is that it's a measure of systemic

11 weight loss, and people lose weight differentially.

12 So even some of the women may have lost significant

13 weight in their breast and not have it reflected in

14 their total weight. But a start would be to look

15 at the magnitude of weight loss in some of those

16 cases.

17   DR. PIANTADOSI: I might just add,

18 hypothetically, this is an answerable question from

19 the data. I don't want to draw the sponsor into

20 this particular discussion, but I would be

21 surprised if they hadn't already done the relevant

22 analyses and don't know the answer to that.

1   DR. THOMAS: I was just going to add one

2   comment about detection bias for the bladder

3   cancer. Because this drug causes increased urinary

4   tract infections, it's quite possible that subjects

5   were getting urinary screening in the treatment

6   group because they had a treated urinary tract

7   infection, and then as a result would have a

8   follow-up urinalysis, which is customary in the

9   United States. I'm not sure if that's the same

10   custom around the world, but it probably should be.

11   As a result, hematuria might have been picked up at

12   a microscopic level, where the usual standard of

13   care would be not to do a urinalysis that often.

14   So there is a potential detection bias as

15   for the bladder cancer. I'm not sure why it's only

16   men and whether there should have been some impact

17   in women as well.

18   Dr. Kaul?

19   DR. KAUL: I agree with Dr. Piantadosi about

20   detection bias. The magnitude of the detection

21   bias is typically in the range of a risk ratio of

22   1.1 to 1.3, and what we see here far exceeds that.

1   And although the numbers are small, the applicant

2   or the FDA could have done some bias-mitigating

3   analyses, where, for example in bladder cancer, you

4   can use the composite of cancer in hematuria or do

5   a time-dependent covariant analysis after

6   hematuria, looking at the risk of development of

7   cancer. But the numbers are probably too small, I

8   believe.

9   Your discussion about infection, if that

10 were true, then the frequency of UTI is about

11 tenfold higher in females, and yet we don't see any

12 bladder cancer, in fact, attributable to the

13 typical gender predilection for transitional cell

14 bladder cancer, which is about 4- to 5-fold higher

15 in males than females? Or are there any gender

16 differences in the pharmacokinetic, pharmacodynamic

17 properties of this drug, or gender differences in

18 the distribution of risk factors for bladder

19 cancer? I mean, those types of analyses, perhaps,

20 might have already been done, or if not, should be

21 done as an exercise in mitigating bias.

22   DR. THOMAS: Dr. Veltri?

1   DR. VELTRI: Yes. Clearly, there could be

2   some selection/detection bias here, but it seemed

3   like most of the infections, both urinary and

4   genital, were in females as opposed to males.

5   Also, one can look at, of those who had infections,

6   I think those patients -- was that the reason why

7   further investigations in those were the ones who

8   developed the bladder cancers. I think it's a

9   little bit more difficult for the breast cancers,

10   for what was stated before. But, certainly, it

11   could be part of the detection/selection bias.

12   DR. THOMAS: Dr. Strader?

13   DR. STRADER: Can I ask a question of the

14   FDA? Unlike the hepatotoxicity, where there's one

15   patient that we see, in this instance, there are a

16   number of patients. Is there some post-marketing

17   monitoring that could be done that would

18   potentially help to mitigate the numbers of cancers

19   that we see? Is there something that we could do

20   because of the numbers of patients with these

21   cancers?

22   DR. IRONY: I'll take the first stab, and

1   then I'll ask my epidemiology colleagues to also

2   chime in. What the applicant had proposed here is

3   to continue to monitor for those cancers, for

4   breast and bladder cancer, in the currently ongoing

5   trials, on those long-term extensions in the

6   randomized control trial to assess either

7   cardiovascular safety or potential cardiovascular

8   benefit, to continue to assess the risk of bladder

9   cancer.

10   Those are large and long trials, but

11   relatively small to detect hazard ratios; that we

12   want to exclude the risk, in addition to conducting

13   these pharmacoepidemiologic studies within a year

14   if dapagliflozin gets approved, and then monitor

15   long term; and depending on the uptake of the drug

16   on the market, how much new users of dapagliflozin

17   versus new users of other anti-diabetic drugs as

18   comparators would be used, try to evaluate on a

19   regular basis the accruing rate of those cancers.

20   So I wanted -- maybe, Christian, if you want

21   to, comment on the proposed pharmacoepi study.

22   DR. HAMPP: Dr. Strom, on behalf of the

1 sponsor, already indicated that they conducted a

2 study with Kaiser Permanente data on pioglitazone

3 in bladder cancer. And it took a couple of years

4 to deliver statistically significant results. That

5 might be the same case with this drug, and that

6 might even be optimistic, given market penetration

7 of pioglitazone.

8   As far as alternatives are concerned, we

9 often rely on spontaneous reports of adverse

10 events, which is not a very good approach for

11 cancer because physicians often don't relate cancer

12 to remote exposure to a drug.

13   DR. THOMAS: Dr. Brittain?

14   DR. BRITTAIN: Yes. I just wanted to know,

15 with respect to the clinical trial that's been

16 proposed, if there's any idea how -- maybe you said

17 it and I missed it -- how large that study would be

18 and how long term, because these are fairly rare

19 events, and I'm a little concerned about how

20 definitive that would be.

21   DR. IRONY: Yes. We don't have any final

22 protocol for a study. But, in general, those are

1   studies not powered for -- it depends on the intent

2   of the study.

3   In those cases, the study would not be

4   powered to detect a hazard ratio of greater than

5   two, for example, for either bladder or breast

6   cancer, or both. This proposed randomized trial is

7   to address more the cardiovascular risk in major

8   cardiovascular adverse events. So those are

9   not -- it's hard to tell what the "n" should be.

10   DR. THOMAS: Dr. Kaul?

11   DR. KAUL: I think that's a key question. I

12   mean, what size trial is required to detect or rule

13   out a cancer risk? I mean, I agree with the

14   sponsor and the FDA that more data are needed to

15   adjudicate the uncertainty and risk, but I remain

16   doubtful if post-marketing evaluation, including an

17   outcomes trial, would be able to resolve this

18   matter.

19   I mean, if you're looking at an incident

20   cancer rate of about 1 percent per year and you

21   want to rule out a 50-percent increase in risk, we

22   are talking about somewhere, a trial of almost

1   30,000, if not greater. And I don't see that

2   happening if you want to eliminate the confounding

3   by indication. But if you're trying to design an

4   observational trial, I heard Dr. Strom mention

5   something to the amount of three- to fourfold

6   larger than the pioglitazone, which would be

7   somewhere around the neighborhood of 100,000

8   patients. So perhaps that's doable, but are the

9   data going to be as credible as a randomized,

10 controlled trial? I mean, these are questions we

11 have to deal with.

12   DR. THOMAS: Dr. Piantadosi?

13   DR. PIANTADOSI: Just a point of

14 clarification. Were you suggesting that the drug

15 would be available only on such a study? Or would

16 such a study be done in the milieu of a marketed

17 drug?

18   DR. DUNN: The applicant was proposing the

19 study to be done on the marketed drug.

20   DR. THOMAS: Dr. Kaul?

21   DR. KAUL: I have a question for

22 clarification, both of the FDA and of the

1   applicant. According to the diabetes

2   cardiovascular guidance, once you have excluded an

3   unacceptable increase of greater than 1.3 hazard

4   ratio, a post-marketing trial is not required. So

5   why is the applicant proposing a cardiovascular

6   outcome trial? Are they trying to prove that this

7   drug is protective, or are they trying to propose

8   that they want to further clarify the

9   cardiovascular safety?

10   DR. PARKS: In reference to the diabetes

11   guidance, to be able to rule out the definitive

12   level of risk of 1.3, there's also -- and I don't

13   have the guidance here in front of me. You

14   probably do. But there's also a section, if there

15   are no other safety concerns, in general, a post-

16   marketing study is not required.

17   So certainly in this situation, the company

18   is proposing to do a definitive cardiovascular

19   outcomes trial. The primary objective, and the

20   company can correct me if I'm wrong here, is to

21   first establish cardiovascular benefit.

22   Certainly, built into that study could be

1   assessing other safety concerns that have been

2   raised at this meeting today. And in a prospective

3   trial, it may address, perhaps, some of the

4   concerns here of seeing these imbalances in perhaps

5   an ad hoc basis. It may address some of those

6   concerns about detection bias and whatnot, that can

7   help at the end of the day if the trial does meet

8   its primary objective to weigh out benefit and

9   risk.

10   But to get to your first question, even

11   meeting 1.3, if there are other safety concerns,

12   that may offset just the 1.3, Additional studies

13   may be required.

14   DR. KAUL: But the question I have is that

15   the cardiovascular outcome trial that they are

16   proposing, and we have not heard anything about the

17   details of that trial, will that be large enough,

18   sufficient enough to rule out this credible safety

19   concern, which is the cancer risk?

20   DR. PARKS: That is correct. You have not

21   heard about that because we have not actively

22   discussed this. The company has proposed this to

1   the agency, and as you've also heard, if this

2   product is approved, it will be a required trial.

3   Clearly, all the concerns that have been raised

4   here would need to be built in on whether or not

5   such a trial can be designed to feasibly address

6   not only cardiovascular safety or benefit, but also

7   all these other safety concerns.

8   DR. THOMAS: Would the sponsor like a brief

9   comment about this?

10   DR. SVANBERG: I'll ask Dr. Daniels to

11   address the discussion which just took place.

12   Dr. Daniels?

13   DR. DANIELS: To specifically answer your

14   question, Dr. Kaul, the design of the CV outcomes

15   study is a hypothesis testing of improvement or

16   reduction in MACE events. But as I also said in my

17   introduction, we think, within that study, you can

18   adjudicate some additional uncertainties,

19   particularly at the level of malignancy, but not as

20   you indicated at the level of specific

21   malignancies.

22   We do believe, and Dr. Strom came and talked

1   about that, that that is a role of the

2   observational trials that we have proposed, and are

3   in your briefing book, to make sure that they are

4   large enough from the beginning and that it starts

5   at a day of authorization and not somewhat later,

6   because we both, FDA and BMS, take the signal in

7   malignancy very serious for breast and bladder

8   malignancy.

9   So those studies will be large enough. Our

10   belief is within two to three years to adjudicate

11   the issue more completely. And so it's really a

12   complementary set of pharmacovigilance and large

13   randomized clinical trials that we think will more

14   fully address the noted imbalance, consistent I

15   think with the legacies of both companies to do the

16   right thing for patients.

17   DR. THOMAS: If there are no further

18   comments, I'll summarize. I'm actually not going

19   to summarize Dr. Piantadosi's elegant comments

20   because I probably will not do them justice.

21   [Laughter.]

22   DR. THOMAS: So I'll summarize everyone

1   else. There's uncertainty about the data that's

2   presented in terms of risk. The issue of detection

3   bias, there clearly could be some detection bias

4   for breast cancer if the subject's lost weight and

5   it was easier to detect, by mammogram or other

6   techniques, a breast cancer mass.

7   For bladder cancer, there could be a

8   detection bias based on the frequency of urinary

9   tract infections, resulting in testing for

10 hematuria because of that. However, the detection

11 bias probably does not explain the overall risks

12 that we see in this study, in terms of the numbers

13 of cases.

14   For the urinary testing, it would be then

15 surprising, because most of the participants who

16 developed urinary infections were women. There

17 were no cases in women, and that could be explained

18 by the biological plausibility that this is more

19 common in men for transitional cell cancer.

20 However, this should bring up some questions about

21 if there are gender differences, mechanistically,

22 that may cause this imbalance. As opposed to

1   concerning an imbalance of baseline risk factors,

2   it was felt that this was covered by the sponsor

3   and there does not seem to be any apparent

4   differences in baseline risk factors throughout the

5   trial, in terms of these cases.

6   The results are very concerning, and a large

7   trial probably will have to be done of some form to

8   look at this with very strict and stringent

9   assessment of risk factors screening to see if this

10   is a real risk for cancer or if this is something

11   that's a signal that will go away with further

12   investigation.

13   A variety of factors can play a role in

14   detection bias. In addition, for breast cancer,

15   besides weight, one that was brought up was also

16   dehydration. And since this drug or medication

17   causes dehydration, at least in some subjects, that

18   hydration status should be looked at, at the time

19   of testing.

20   It was also felt that some of this data

21   could be addressed with data that's already

22   present, some of this concern, and that the sponsor

1   might have been doing this already, looking at

2   previous mammograms and other terms of detection

3   for cancer. That could be helpful to the FDA. It

4   would require a very large trial. Dr. Kaul

5   estimated somewhere between 30 [thousand] and

6   potentially up to 100,000 subjects to answer this

7   question.

8   The sponsor does seem willing, as part of

9   their cardiovascular trial, to look at this further

10   because of the seriousness of the issue for breast

11   and bladder cancer.

12   We'll now go onto question number 4, other

13   safety findings. Please discuss the clinical

14   significance of the following in the type II

15   diabetes mellitus population: A, increased

16   genital/urinary infections associated with

17   dapagliflozin therapy; B, bone safety concerns; 3,

18   any other safety issues identified in the

19   pre-marketing application.

20   If anyone has any questions, otherwise --

21   [No response.]

22   DR. THOMAS: Okay. I will start.

1   For the first subject, increased

2   genital-urinary infections associated with

3   dapagliflozin therapy, clearly, there's imbalance,

4   infections, between the two groups, placebo and

5   treatment group.

6   When you look at the Kaplan-Meier plots,

7   they're looking at the first event. There also

8   seems to be an increase in secondary infections.

9   None of these were really significant in terms that

10 there are very few cases that reached the level of

11 pyelonephritis. However, you have to remember that

12 these are short trials, 24-week extensions, with a

13 smaller number of subjects up to one year and even

14 smaller up to two years.

15   How does this equate into long-term use of

16 this medication? One concern that I always worry

17 about is the antibiotic resistance. It's not

18 necessarily related to the short-term usage of this

19 medication, but if a particular individual has

20 repeated infections, do they develop antibiotic

21 resistance? And how is that treated, and how is

22 that passed onto other subjects in their community?

1   [No response.]

2   DR. THOMAS: All right. I will keep going

3   on.

4   Bone safety concerns. There were no obvious

5   bone safety concerns from the data presented by the

6   sponsors. They did have one-year dexa data from a

7   further body fat morphometry analysis. However,

8   there were no bone markers presented at this

9   meeting. I think it would be important to know how

10 markers of bone turnover are affected over the

11 course of several years.

12   I think one year is probably quite short to

13 look at fracture in this population -- you probably

14 need several years of data to look at

15 fracture -- and also to look at bone density by

16 dexa.

17   Dr. McBryde?

18   DR. MCBRYDE: Actually, the bone safety, I

19 had a couple of thoughts and concerns about. And I

20 have to admit, even as a nephrologist, I'm not a

21 huge fan of metabolic bone disease, but I've always

22 been somewhat concerned about the use of dexa in

1   obese patients. In looking at a lot of the data,

2   there were BMIs of 33 to 38 for the subjects. I

3   have some concerns about whether or not that's

4   truly giving an adequate representation of lean

5   body mass, the fat-free mass, but also bone mineral

6   density.

7   I think Dr. Seely had asked earlier about

8   the number of people reported with the familial

9   renal glucosuria. And looking at some of the

10   reviews on that, hypercalciuria has been described

11   in that population. I noticed that there was no

12   change in calcium, so I assume that that's total

13   serum calcium. But there's no comment on any

14   potential changes in ionized calcium.

15   I did hear a discussion briefly about

16   urinary potassium and urinary magnesium excretion,

17   but nothing on urinary calcium. But certainly, if

18   there's hypercalciuria and dexa's screening for

19   bone mineral density with possible inadequate or

20   inaccurate measurements of bone mineral density, I

21   don't know that I think that the risk fracture has

22   been well defined in this population.

1   So I just wanted to sort of throw that out

2   that I have some concerns there, although I don't

3   have anything firm to hang it on. A lot of that,

4   again, is hampered by an absence of data provided

5   by the sponsor, at least in the preclinical testing

6   of the drug.

7   DR. THOMAS: Dr. Smith?

8   DR. SMITH: Yes. I absolutely agree with

9   those comments. And I, too, have great concerns

10   about self-delusion, that the duration of

11   observation thus far has anything to do with the

12   kinds of concerns that any thoughtfulness

13   concerning this drug and the impact on the skeletal

14   system it might have. And I think we need guidance

15   in terms of how the FDA thinks that the continued

16   surveillance could be built into any kind of post-

17   marketing activities required of the sponsor.

18   DR. THOMAS: Would someone from the FDA want

19   to comment on that?

20   DR. AVIGAN: Clearly, there are different

21   options in the post-market in terms of the

22   intrusiveness, or the proactiveness of

1   pharmacovigilance, and also epidemiological studies

2   that are available. So there's a toolkit. And to

3   some extent, it's one where we would look at what

4   are the burning questions that need to be answered,

5   and how can they be answered in a practical manner,

6   and work out the arrangement from the advice that

7   the committee gives, with the sponsor.

8   So there's a kind of balance between the

9   information that's needed and the tools that are

10   available in a practical manner. But we would

11   entertain pharmacoepidemiologic studies if they're

12   necessary, observational studies, as well as

13   proactive pharmacovigilance and spontaneous report.

14   Ascertainment would follow up to reporters for more

15   clinical information if it's a key piece in the

16   equation.

17   DR. THOMAS: Well, I think if there are any

18   other safety issues identified in the pre-marketing

19   application -- I will bring back up two that were

20   mentioned earlier by the panelists, which are

21   related. One is the overall risk of dehydration

22   and potential renal dysfunction and how it is

1   classified by the sponsor, whether it's volume

2   depletion or renal dysfunction. That might be a

3   concern when this is used in a larger population.

4   The other related risk is the use of diuretics,

5   which can promote dehydration, and especially in

6   certain populations like the elderly, that may be

7   more pre-disposed to hypotensive episodes.

8   There was also -- I'm personally concerned

9   about the comment of use with loop diuretics, that

10 maybe a smaller dose should be used, 5 milligrams

11 in patients with loop diuretics. Usually, many of

12 us use loop diuretics in people who already have

13 impaired renal function, as a choice as opposed to

14 hydrochlorothiazide. So then you have the

15 additional issue of is there efficacy along with

16 the safety issue.

17   There was also an earlier concern brought up

18 about the elderly. Specifically, though there is

19 some advantage, potentially, by having lower rates

20 of hypoglycemia in the elderly. We're really not

21 sure about the efficacy and these other side

22 effects that may be a problem.

1   Dr. McBryde?

2   DR. MCBRYDE: I have to say, I didn't see

3   any of this, other than the weight loss, in the

4   packages. But I did want to follow up on

5   Dr. Savage's earlier comment because certainly in

6   the elderly, one of the concerns I would have is

7   that, especially in subjects with normal renal

8   function, you'd be looking at the loss of an excess

9   of 100 grams of glucose in the urine, daily. And

10   that may be 300, 400, 500 kilocalories per day.

11   And what may happen to patients, particularly in

12   terms of their other nutritional status, there's no

13   data on protein catabolic rate to see if the

14   patients are put into a negative nitrogen balance

15   in order to maintain energy status or even ketosis

16   as a result of the loss of so much carbohydrate

17   calories. It maybe makes sense in terms of

18   reducing the hemoglobin A1c, but in terms of the

19   overall nutritional balance of the patient, I would

20   worry that it may cause not so much a malnutrition

21   as a dysnutrition in those subjects.

22   DR. THOMAS: Dr. Savage?

1   DR. SAVAGE: Yes. I'd like to sort of

2   second that basic concern. I think that the last

3   10 minutes or so, we've been talking about several

4   additional unknowns that we don't know for certain

5   how significant they might be, if this drug were

6   used for five years or something of that sort.

7   Certainly, if a post-marketing study was

8   done, there are a series of these questions that

9   need to be thought through and built into it right

10   from the start. And I would also, I think, stress

11   the comment that was made earlier, that if they

12   were going to do this type of study, it would be

13   designed so that it could start right away, and it

14   would give answers within a few years, because I

15   was here a year or a year and a half ago and heard

16   a study described that was looking at a very

17   important question, but wasn't going to produce a

18   definitive answer for I think it was seven years or

19   something after the time the study got started.

20   And it would be a shame if that situation repeated

21   itself.

22   So I think there are a whole host of

1   questions that we need to know more about. They

2   could be built into a post-marketing study. I

3   realize that the data on cancer, you can look at in

4   different ways and say maybe these are some sort of

5   picking up cases that already existed and so forth.

6   But the problem is, if you make a mistake on making

7   a drug widely available that causes cancers, it's

8   going to do a lot more harm than if you have to

9   make some adjustments in what elderly people would

10   be optimal and so forth, if you designed the right

11   study to get a quick answer.

12   So I'm concerned about the bigger issue of

13   more serious things that have been identified, but

14   I think there are a lot of other questions that

15   would also need to be carefully thought through,

16   and it would have to be done fairly quickly to get

17   such a study underway fairly promptly if the FDA

18   decides to go ahead with this.

19   DR. THOMAS: Dr. Seely?

20   DR. SEELY: Just to put the glucose loss in

21   urine into perspective, so maybe we wouldn't be

22   prescribing this to our lean and underweight type I

1   diabetics, but most of our diabetics we're trying

2   to put them in a negative calorie balance, and we

3   do it by telling them to cut back on their

4   calories.

5   We don't know that we're doing a great job,

6   when we tell people to cut back on their calories,

7   of balancing every nutrient and vitamin that

8   they're taking. So I just don't view that as a

9   major issue. When you think about acarbose, where

10   there are drugs where we're trying to get calories

11   not come in the body, where we're trying to make a

12   calorie deficit.

13   DR. THOMAS: Dr. Irony?

14   DR. IRONY: Yes. I wanted to ask

15   Dr. McBryde and follow up on this issue of the

16   potential dysnutrition that you mentioned. What

17   would you propose? It's possible you heard from

18   them that they are conducting a study and they just

19   presented interim data on this fat mass versus lean

20   body mass, and it changes over a year, and this is

21   continuing, what other specific endpoints would you

22   have to ensure that those patients are not

1   malnourished or dysnourished?

2   DR. MCBRYDE: I think you could do it a

3   couple of ways and depending upon the precision and

4   accuracy of the measure used, you could do it on a

5   smaller sample of subjects versus a much larger

6   sample of subjects. I'm not sure dexa would be my

7   choice for any of those measurements.

8   If I was really, truly interested in

9   something such as lean body mass, I might consider

10   something like MRI imaging and quantitative, simple

11   body anthropometric measurements as well, serum

12   markers of nutrition. They have data that they've

13   included in some of their publications of 24-hour

14   urine collections for creatinine clearance. You

15   can also do a urine urea nitrogen on that and get

16   an estimate of their protein catabolic state that

17   could be combined and compared against what their

18   serum albumin, pre-albumin, and other nutritional

19   markers may be.

20   So I think that there's a variety of

21   different techniques. Some are much more accurate

22   than others, but I think, in the obese population,

1   I don't -- and certainly, I'm not an

2   endocrinologist, and in the nephrology field, we

3   don't do many of these. I don't think that dexa

4   really is the ideal choice for looking at body

5   composition or body compartments.

6   DR. THOMAS: So if there are no further

7   comments, I'll summarize the discussion for

8   Question 4. Concerns were brought up. The

9   increased genital-urinary infections, we know that

10   it's increased in women and increased with the

11   drug. There would need to be longer-term data to

12   see if there's recurrence and any more severe

13   infections, which is not apparent at this time in

14   the data presented by the sponsor.

15   In terms of bone safety concerns, it was

16   felt that one year is too short a time to really

17   assess this, plus many of these patients are obese

18   and they may have some increased bone density. And

19   as a result, bone density measurements by dexa may

20   not be sufficient also for this analysis.

21   Probably, it would be worthwhile to have markers of

22   bone turnover and longer follow-up for fractures

1   and changes over time in this population.

2   In terms of other safety issues or issues

3   identified about hypotension, or dehydration, and

4   changes in renal function -- also about the fact

5   that there is a loss of calories in the urine,

6   which may not be an issue in patients who are

7   overweight or obese with type II diabetes. But in

8   some subjects, where there are issues of

9   nutritional balance, further studies could be done

10   to look at nutritional balance such as 24-hour

11   nitrogen or protein clearance, body composition by

12   other techniques than bone density, such as MRI,

13   and serum markers of nutrition.

14   The final comment is that there are many

15   unknowns in some of these safety findings.

16   However, they were less concerning than the two

17   major ones that were brought up before, which are

18   breast and bladder cancer and hepatic safety.

19   We will now move onto the voting question.

20   The voting question is, does the efficacy and

21   safety data provide substantial evidence to support

22   approval of dapagliflozin as an adjunct to diet and

exercise to improve glycemic control in adults with

type II diabetes?

You'll be able to vote yes or no. And then

after we have the vote concluded, we'll go around

the panel, and if you voted yes, do you recommend

any further data be obtained post-marketing? If

no, what further data should be obtained?

We'll be using an electronic voting system

for this meeting. Each voting member has two

voting buttons on your microphone, yes and no.

Please vote by pushing the button located

immediately below the corresponding letter, where

it says yes and no, and, again, firmly push the

same button three times.

After everyone has completed their vote, the

vote will be locked in. The vote will then be

displayed on the screen. I'll read the vote from

the screen into the record, and then we will go

around the room, and each individual who voted will

state their name, and vote into the record, as well

as the reason why they voted as they did.

If there is no further discussion, we'll

1   start the voting process.

2   Are we ready to do that? So please press

3   the button, either yes or no, three times on the

4   microphone, that corresponds to your vote. You

5   will have approximately 20 seconds to vote. Please

6   press the flashy button firmly. After you've made

7   your selection, the light will continue to flash.

8   If you are unsure of your vote, please press the

9   corresponding button again.

10   [Vote taken.]

11   DR. THOMAS: I am going to read the results

12   of the vote into the record. Six members of the

13   panel voted yes. Nine members of the panel voted

14   no. And we didn't give you an option, so no one

15   voted abstain or no voting.

16   I will now read into the record the names of

17   the individuals who voted yes or no. Dr. Brittain

18   voted no. Dr. Capuzzi voted no. Dr. Felner voted

19   no. Dr. Gregg voted no. Dr. Hendricks voted yes.

20   Dr. Kaul voted yes. Dr. McBryde voted no.

21   Ms. McIntyre voted no. Dr. Piantadosi voted yes.

22   Dr. Savage voted no. Dr. Seely voted yes.

1 Dr. Spruill voted no. Dr. Strader voted no. And

2 myself, Dr. Thomas, voted yes.

3   We will now go around the room and have all

4 the voting members, in turn, read into the record

5 their vote and the reasons for their vote; as

6 explained earlier, if voted yes, recommending any

7 further data be obtained post-marketing, and if no,

8 what further data should be obtained.

9   Dr. Seely, we'll start with you first.

10   DR. TRAN: If you could state your name

11 again and your vote.

12   DR. SEELY: Ellen Seely, and I voted yes for

13 approval. I did that based on, as an

14 endocrinologist, feeling that although there's a

15 scare factor to the word cancer, seeing patients

16 with diabetes, and it's a devastating disease, I

17 don't feel that we have effective treatments

18 currently available in terms of enough of an

19 armamentarium, and that finding anti-diabetic

20 agents that are weight-neutral is really going to

21 be a huge advance. I think the drug should be used

22 in patients with normal or only mild renal

1   dysfunction, and that they should be overweight or

2   obese.

3   Should I talk about post-marketing now or

4   later?

5   DR. THOMAS: You should talk about that.

6   DR. SEELY: So I feel that there is a good

7   reason to expect detection bias since both the

8   bladder and the breast cancer findings. And I

9   think that it's going to be impossible for the

10   sponsor to power a study with those being the

11   outcomes. And if we ask companies to power for

12   those outcomes, it'll mean we're not going to have

13   new drugs coming on the market to treat a lot of

14   the chronic diseases that we have.

15   So although surrogates are not as good, I

16   think looking at some of the potential reasons why

17   there might be an unmasking of diagnosis of both

18   breast and bladder cancers, it would be important

19   to do in post-marketing studies.

20   I think looking at the impact of the

21   medication on albuminuria is really going to be key

22   as well for the post-marketing studies. And I

1   think a prospective study that can occur post-

2   marketing, but it would need to be a controlled

3   prospective study, is to look at patients with

4   moderate renal impairment to see whether any

5   patients in that subclass might benefit.

6   DR. THOMAS: Dr. Savage?

7   DR. SAVAGE: I voted no. I actually agree

8   with many of the things that Dr. Seely has said and

9   I've been going back and forth, listening to the

10   discussion today. It seems to me that there is

11   some additional data that should be pulled together

12   in some way before this drug is released for

13   widespread use in potentially millions of people.

14   I mean, if the word gets out there that

15   there's a drug that has shown an effect in terms of

16   lower risk of cardiovascular disease, and that it

17   can prevent elderly people from having to take

18   insulin and so forth, it could become a very

19   popular and widely-used drug.

20   I just feel that the discussion that's gone

21   on today left me thinking that there are questions

22   that can be answered, not getting definitive

1   endpoints, say, on cancer risk, but if another

2   study was done and it showed the same sort of non-

3   significant pattern, I'd be much more

4   concerned -- I'd feel much more certain that it

5   might be real than right now, I'm just uncertain

6   because I think some of it may be a selection bias.

7   Then the other issue that I think is

8   pertinent to the United States is the absence of a

9   substantial number of people from the minority

10   groups that are very common in this country, that

11   probably will be of similar result, but I'm not

12   sure that we have enough data to say that for

13   certain.

14   Then the final thing is, as I said in my

15   question earlier, I think it could be a very useful

16   drug in older people, but I'm not sure how

17   effective it will be because of the combination of

18   declining renal function in the elderly and so

19   forth.

20   So that's why I voted no. It was not a

21   clear-cut thing, where I felt absolutely certain

22   that the only possible answer was no.

1   DR. FELNER: Eric Felner. I voted no. I

2   actually like this drug. I mean, it seemed to be

3   very efficacious. It's a different mechanism of

4   action. It does the thing that I think -- although

5   I don't see as many type II patients as the adult

6   colleagues here. But, I mean, it promotes weight

7   loss, and it improves A1c, and add-on therapy looks

8   great.

9   I think that alone, thinking of just that,

10   actually, before coming to the meeting, or knowing

11   some of that information, I didn't want to get a

12   skewed view in a sense, without even thinking about

13   the risk or the side effects. And there's

14   something about the breast and the bladder cancer

15   that has bothered me.

16   I think just knowing some of the baseline

17   information, which I think I was trying to get to,

18   or some of the points that Dr. Seely had brought up

19   about the weight loss, actually possibly bringing

20   it out, if those things can be identified a little

21   bit better, I would love to see this drug get

22   approved, as long as some of those things could be

1   at least looked at. And I don't think it's going

2   to take a very large study, as some were worried

3   about before.

4   DR. CAPUZZI: Yes. Dr. Capuzzi. I voted

5   no. Frankly, I came in here on the fence, and I

6   was leaning toward yes until I didn't hear enough

7   to be convincing about this. I want to make a

8   couple of statements.

9   First of all, I think, as has been expressed

10   before, it's valuable to have an agent that does

11   not either sensitize insulin or substitute for

12   insulin and work in the bloodstream. It just gets

13   rid of glucose. And what you see here is there

14   doesn't seem to be any untoward effect of having

15   this glycosuria and seeing an increase in UTIs or

16   anything like that. And it might be useful in the

17   elderly, who have a shorter time to live, really,

18   although we never know, obviously. And it would be

19   easy for them to use. And with all the agents that

20   are now being produced, such as the hormonal

21   analogs and all these fancy creative peptides, this

22   is not going to make a major difference this way.

1   However, the thing that is persuading

2   me -- of course, there are some things that are

3   missing in this program, and it's kind of routine

4   in the pharmaceutical industry. We don't have any

5   pharmacokinetic data or efficacy safety data on

6   patients who have congestive heart failure as an

7   issue, with everything else relatively okay, renal-

8   compromised patients, hepatic-compromised patients,

9   and a study in the elderly.

10   I mean, they're very basic to do in any

11   program, let alone a program like this, which kind

12   of targets the elderly. So those things are

13   missing. And there wasn't much said about protein

14   binding, GI absorption, what interferes with it,

15   what promotes it, what concomitant drugs you might

16   or might not use. And nowadays, anybody can get a

17   variety of different agents, depending on their

18   insurance and the availability of agents.

19   So I think that while I really like the

20   concept, we just don't have enough right now, in my

21   opinion, to ensure safety and efficacy, and how to

22   use it. How are you going to explain to the

1 clinicians and others who are -- I don't want to

2 say non-clinicians, but lots of people are treating

3 patients nowadays. You've got to have some really

4 clear-cut safety features here, what the individual

5 can do, what kind of patient is best suited, and we

6 just don't have those data.

7   I hope that the company can produce that

8 because I think this would be a great way to

9 further lower the blood sugar, however

10 unconventional this is. And this just reminds me

11 of adding a bile acid binder or ezetimibe to a

12 statin. You're going to get an additional effect,

13 although I don't want to talk about those drugs.

14   But it's taking another mechanism and

15 dropping it down. And since a lot of the patients

16 will be elderly, I think you have to do some kind

17 of a study in the elderly to see if they can

18 tolerate it, if they can think when they're taking

19 it. And our population is growing much more into

20 the elderly category compared to 20 or 30 years

21 ago. So I just don't feel that we can safely do

22 this right at this time, and yet I very sincerely

1   hope that this can be worked out.

2   DR. BRITTAIN: Erica Brittain. I voted no,

3   but it was the closest of calls. I changed my mind

4   about four times in the last 10 seconds. And I am

5   very sympathetic with a lot of the comments that

6   Dr. Seely made. And I agree that the level of

7   evidence about the cancer is fairly weak evidence.

8   It's just that the uncertainty is still there.

9   So like I said, I really am on the fence

10   about the issue of whether you approve now versus

11   later, when there's more information. What I think

12   is most important is to get more information. And

13   even in the course of the randomized study, that

14   could be monitored as it's ongoing. And if the

15   news looks good early on, perhaps that could be

16   used to change -- depending on what decision is

17   made now, or vice versa. So it wouldn't

18   necessarily have to wait for eight years or however

19   long it would take to do the study.

20   But anyway, again, I really think the

21   important thing is to get the information, and I

22   could go either way on the approval now versus

1   later.

2   DR. THOMAS: Abraham Thomas. I voted yes.

3   Just a few comments first. This is, to me, one of

4   the first examples of a medication that was

5   developed for diabetes that works in a different

6   way, in the sense that almost all of the

7   medications you have for diabetes take

8   pathophysiology and try and improve it to normal

9   physiology.

10   This actually is taking physiology and

11   making it into pathology by increasing glucosuria,

12   which is a strange paradigm for a new medication.

13   I think, as a result, there's some concerns about

14   the side effects that we see. The liver, bladder,

15   and breast issues are very concerning, but I felt

16   there's no way of knowing the answers unless we

17   study more subjects.

18   I just think it's not realistic for drug

19   development to do that pre-marketing. The scope of

20   this trial may be 30,000 to 100,000 subjects. It

21   may need to require databases that are being

22   developed. I know the FDA is developing early

1   warning databases, large groups like Kaiser, other

2   HMOs. That's really the only way they're going to

3   get at this answer for some of these, is from more

4   data.

5   Clearly, we didn't have the data to answer

6   these questions, as you can tell by the panel. So

7   in addition to those, I think, other lesser issues,

8   which would be more of concern later on, they

9   really do have to be answered at the beginning.

10   Some of these will be called minor issues, but

11   actually can be very inconvenient to patients, more

12   infections, fracture rate, dehydration that could

13   cause syncope, leading to injuries. These need to

14   be answered as well.

15   There are a few quality-of-life issues,

16   which I think about as nocturia. We treat our

17   patients with diabetes. We eliminate their

18   glucosuria. They get a good night's sleep. It's

19   not clear at all from the data that that's what

20   we're going to do with these subjects.

21   The way the study would have to be analyzed,

22   from the clinical trial data, you'd never be able

1 to answer this question because you start off with

2 glucosuria and nocturia. You have a medication

3 that causes it at the end, and then you have a

4 placebo group that has it as well. So, of course,

5 there's not going to be a significant difference.

6 You really have to answer this question. I would

7 suggest doing that as part of these follow-up

8 studies, quality-of-life sleep issues, nocturia, in

9 addition to monitoring for fractures. But the key

10 question is going to be the long-term follow-up for

11 breast and bladder cancer, and for the liver

12 disease. We need more data to see that signal.

13   Finally, there was mention about the fact

14 that there is a familial kindred that has this

15 disease with probably 100 individuals. I just want

16 to remind everyone, we have a similar situation

17 with people who have familial hypertriglyceridemia.

18 They have markedly elevated triglycerides but do

19 not carry coronary risk. However, if you were to

20 extrapolate that to other populations of elevated

21 triglycerides, that relationship does not hold, as

22 other groups of elevated triglycerides do have

1   increased coronary risk.

2   So I am not at all reassured by the fact

3   that there is a family and other individuals with

4   mutations in this transporter that have glucosuria.

5   And so I don't think that's a way to reassure

6   ourselves as to the safety of this class of

7   medications.

8   DR. GREGG: I voted no as well. I actually

9   thought -- I think this is a very encouraging drug

10   from an A1c efficacy standpoint and possibly even

11   effectiveness in cardiovascular disease reduction.

12   I saw some concern in terms of the lack of clarity

13   of what segment of the population would not benefit

14   from the drug, but I don't think that was a huge

15   factor. The big one for me, really, was the

16   magnitude of the risk ratio for the cancers.

17   Although we clearly can't say, from the data, that

18   this drug causes the cancers, if this was a risk

19   ratio of 1.5 or 2, I think we would have found

20   ourselves able to dismiss it; but with 4 and 5,

21   that wasn't the case.

22   Now, obviously, trials can't prove that the

1 drug is safe, but that's enough of an excess risk

2 that it shows that -- really, that's part of the

3 purpose of phase 2 and phase 3 trials, is to

4 identify a concern that requires more evaluation.

5   So in the end, the list of things that were

6 needed as part of post-marketing surveillance

7 seemed too long, and it implied that we need more

8 pre-marketing surveillance beforehand. So I don't,

9 on the other hand, think that a large, definitive

10 trial is necessary here to make this a viable drug.

11 I think that perhaps with the data that is being

12 collected now in ongoing -- as well as a, perhaps,

13 medium-sized trial, enough to at least tell us

14 whether this experience from these databases were

15 aberrations, random, or essentially noise, I think

16 that that would be enough to make this a viable

17 drug.

18   DR. SPRUILL: Ida Spruill. I voted no. And

19 I agree with all of my colleagues that voted both

20 yes and no. As a diabetes nurse educator, I came

21 into this session excited because here was a drug

22 that had the potentials to lower A1cs, to make you

1   lose weight, to increase the blood pressure. You

2   can take it at any time. And I listened, and I

3   just got kind of perplexed. And as a consumer

4   representative, I listened to the sponsors talk

5   about the design of the study, and I was just

6   disappointed.

7   I was disappointed. Yes, I understand there

8   was a multi-country trial, but I was disappointed

9   that in the United States we're only talking about

10   27 percent of the population, and out of that, less

11   than 5 percent African-Americans, only 1200

12   elderly. And I just was cautiously optimistic.

13   So I made a decision. Like you, I went back

14   and forth and back and forth. And I decided to

15   vote no because I think we need more information

16   for efficacy and the effectiveness of it in a group

17   of people, subgroups of people, who have the burden

18   of diabetes on them. And I think the sponsors did

19   a good job of talking about it, but I was lost and

20   left with feeling a little disappointed that

21   something was missing.

22   DR. PIANTADOSI: Steve Piantadosi. I voted

1   yes because I think that the evidence for efficacy

2   was really quite strong, and the implementation of

3   a new therapeutic paradigm was very good. I

4   obviously am concerned about the weak evidence for

5   a substantial cancer risk.

6   I think that the only way those questions

7   will be answered is from a large study, which is

8   not likely to be completed pre-marketing. I think

9   it's going to have to be a post-marketing study.

10   And I do think the size of that trial will be

11   substantial. For example, the detection of a

12   twofold risk requires 90 events. And if the

13   background frequency is .3 percent, there's your

14   30,000 subjects right there. That's not going to

15   be done pre-marketing.

16   I do believe that from a patient's

17   perspective, it would be a sensible decision to

18   participate in such a study with the potential

19   therapeutic promise of the drug weighed against the

20   possible risk factors, and the trial could be

21   designed in an appropriate way that would make that

22   a perfectly sensible decision to participate.

1   DR. MCBRYDE: I'm Dr. McBryde. I voted no

2   for a variety of reasons. I was quite interested

3   in the drug because of its novel approach to the

4   treatment of diabetes. But coming at it from a

5   nephrology perspective, looking through the

6   package, I think -- I've learned in my career to

7   have a tremendous amount of respect for the

8   proximal tubule of the kidney. On electron

9   microscopy, it is packed with mitochondria, and it

10   is truly a magnificent structure. And simply

11   saying, I'm going to block SGLT2 and it'll have no

12   other effect on the proximal tubule, I think, is to

13   give a tremendous discredit to the function of the

14   proximal tubule.

15   Intracellular sodium potassium and

16   reabsorption in the proximal tubule from the lumen

17   is critical to the function of the sodium potassium

18   ATPase on the basal lateral membrane. That is also

19   critical for maintenance of cellular function as

20   well as other activities.

21   I'm a little surprised that the sponsor

22   hasn't done basic data analysis, basic studies to

1   find out the effects of hypoproteinemia, or

2   proteinuria on the bioavailability of this drug and

3   to see what it does. To me, a drug that you know

4   is 91 percent protein-bound should have never been

5   put into a patient without knowing what's going to

6   happen in hypoproteinemia and proteinuria.

7   We know from numerous drug studies and

8   experience that proteinuria induces drug

9   resistance. If you look at the familial renal

10   glucosuria subjects, many of them are children,

11   because, obviously, they're born with this

12   disorder, and I'm a pediatrician at heart. But

13   they suffer from growth delay. They suffer from

14   chronic dehydration, electrolyte imbalances due to

15   the polyuria. They develop hydronephrosis,

16   natriuresis. They develop hypercalciuria.

17   I didn't see any data presented by the

18   sponsor that they've even looked at it. It's as

19   though they've looked at this packet and felt as

20   though they came at it brand new, and decided to

21   look. And that was a little shocking to me, that

22   just basic information about the drug and the

1   mechanism of action were completely missed.

2   I don't know who they're really targeting

3   here because if we take away the albuminurics, or

4   the proteinurics, and the impaired renal function

5   subjects, is this monotherapy? Is it combination

6   therapy for the newly diagnosed diabetic with

7   uncontrolled hemoglobin A1c with other meds? I

8   don't really understand who they're targeting at,

9   because so many studies were done with so many

10   different populations. It just was too many

11   unknowns about the safety of the drug.

12   Hemoglobin A1c, I was excited to see the

13   improvement in control, but in the presence of so

14   many unanswered questions about the drug and its

15   safety, especially as a new class, and potentially

16   the wide distribution in prescribing practices of

17   this drug, I just didn't think it was quite ready

18   to be used on humans in an uncontrolled manner and

19   left to the post-market environment to get

20   voluntary reporting of adverse events.

21   DR. STRADER: Doris Strader. I voted no. I

22   think that this is an elegant drug, to be able to

1   reversibly inhibit glucose transport in the liver.

2   To a hepatologist at least, it seems brilliant in

3   its simplicity. However, I was struck by the

4   absence of some pharmacokinetic data, as

5   Dr. Capuzzi and Dr. McBryde mentioned, as far as GI

6   absorption, and drug-drug interactions, and

7   evaluations of patients with proteinuria,

8   et cetera.

9   In addition, the issue of hepatotoxicity is

10   always one that's a little bit concerning to me.

11   While I'm not certain that this one case would be

12   enough to disqualify the drug, I think that it does

13   raise some issues about the importance of

14   monitoring patients with liver disease, as most

15   diabetics have, very carefully.

16   The breast and bladder cancers, I can't

17   dismiss as being irrelevant or minor. Admittedly,

18   I don't know enough about these issues, but I was

19   concerned about the fivefold increase and the

20   inability to sort of explain why these happened.

21   Having said that, I realize that it is true

22   it's difficult to do studies on large numbers of

1   patients in a pre-marketing situation. However, I

2   feel very uncomfortable about subjecting the

3   diabetic population to a potential risk in post-

4   marketing studies so that we can get enough numbers

5   of people to evaluate potentially life-threatening

6   complications.

7   We do these studies for a reason, and when

8   we find issues that are concerning, we should not

9   ignore them, but try to find thoughtful ways of

10   being able to balance the benefit of the drug with

11   the potential patient risk. So those are the

12   reasons that I voted no.

13   MS. MCINTYRE: Cassandra McIntyre, patient

14   representative. I voted no, and in my opinion, the

15   sponsor needs to obtain more data about the hepatic

16   safety, breast and bladder cancer, increased

17   genital-urinary infections.

18   I listened carefully to the public speakers

19   who expressed concerns about the unanswered safety

20   risks. Dapa is innovative and could be useful to

21   some people with type II diabetes. At present,

22   patients do not have enough data to make an

1   informed decision. It would be best to address the

2   safety risk concerns before approval rather than

3   have adverse events develop post-market, which

4   could cause loss of the public trust and put lives

5   at risk.

6   DR. KAUL: Sanjay Kaul. I voted yes. The

7   underlying philosophy is that there is an inherent

8   asymmetry in the assessment of efficacy and safety.

9   Efficacy is anticipated. It is prespecified. The

10   studies are adequately powered. The events were

11   adjudicated, and the effect sizes are precisely

12   measured and quantified in pre-marketing trials.

13   On the other hand, safety issues are

14   sometimes unanticipated, not prespecified.

15   Sometimes, they're not adjudicated. Sometimes,

16   they are caught in a delayed fashion. Therefore,

17   they're not precisely measured and quantified. And

18   the risks that were unearthed in this development

19   program were unanticipated and would require a very

20   large trial to adjudicate the uncertainties and

21   risks. And I don't think that is possible. I

22   agree with Dr. Piantadosi, that's not possible to

do that, or feasible to do that, in a pre-marketing situation.

So when you look at the overall benefit-risk profile, there's a modest glycemic control efficacy which, technically speaking, is no worse than what the guidelines recommend as first-line or second-line, i.e., non-inferior to metformin and sulfonylurea, without the liability of weight gain and hypoglycemia.

However, having said that, I think the label should be restricted to normal and mild renal function. The cancer signal is a credible concern to me and I think it merits a boxed warning until we have resolved the uncertainty around it, if it can be done.

For a cardiovascular outcomes study, I think we have to enroll a much more enriched population. Twenty percent of those with a prior history of cardiovascular disease were enrolled in this program. I don't think that's sufficient. My recommendation is that more than half of the patient population should have a prior history of

1 cardiovascular disease. More than half of the

2 patient population should have longstanding

3 diabetes, more than eight to 10 years in duration.

4 And at least more than half of the population

5 should be over the age of 65, and if possible, more

6 than a quarter of the patient population should be

7 over the age of 75.

8   A trial in patients with moderate renal

9 insufficiency is warranted, so if you can

10 incorporate patients with moderate renal

11 insufficiency -- for example, in this development

12 program, I understand only 10 or 11 percent of them

13 had moderate renal insufficiency, and I would look

14 at somewhere around about in the neighborhood of

15 more than one-third of them should have renal

16 insufficiency.

17   So those are my recommendations, and we sort

18 of agonized over it and deliberated. This sort of

19 illustrates the futility of a simple vote count.

20 The vote count here does not give credit to the

21 degree of discussion and deliberation that has

22 taken place. And, fortunately, the FDA pays a lot

1   of attention to the discussion rather than the

2   simple vote count. Thank you.

3   DR. SMITH: Terry Smith, and I voted yes. I

4   have a hard time disagreeing with almost everything

5   that's been articulated here today. And I'm not

6   going to waste everyone's precious time restating,

7   but to say that, for me, this was not an easy

8   decision, one which I think captured more a sense

9   of what is practical in the real world and being

10   mindful of a sponsor who has obviously spent an

11   enormous amount of time and energy generating a

12   novel therapeutic approach, which I think

13   societally we need to encourage.

14   I think they've generated data which are

15   compelling for efficacy. While not profound, I

16   think will be highly complementary to the other

17   tools in our armamentarium to take care of our

18   patients.

19   So the issue is waiting and expecting a

20   rather Herculean set of further trials versus

21   proposing that the agent be considered for approval

22   at this point and highlighting all of the

1   safeguards that make this a reasonable approach.

2   I have a very large number of cons in my

3   pro/con diagram here. I really feel quite emphatic

4   that the sponsor needs to better define the target

5   population, especially the metabolically fragile

6   older patient who might be prone to hypoglycemia.

7   From this agent, either alone or more likely in

8   combination with others that are more likely to

9   cause hypoglycemia, I think that it's imperative

10   kinetic studies be offered, the results of kinetic

11   studies be offered.

12   I'm, like everyone else, concerned about the

13   liver and cancer issues and what is a reasonable

14   target patient with regard to renal function. And

15   I think it's more than imperative that our patients

16   be monitored quite closely as they live longer with

17   the disease.

18   I think ultimately the decision will be

19   judged not in the next year or two years, but way

20   down the line when not just a surrogate of disease

21   like the A1c has been evaluated, but, rather,

22   looking at complications and all of the issues

1   which can shorten the lives of patients with this

2   disease.

3   DR. HENDRICKS: Ed Hendricks. I voted yes.

4   I believe, from the data presented here today, that

5   this will be an effective drug in treating

6   diabetes. As a clinician, I'd like it for three

7   reasons. One, it's an oral drug. Two, it has

8   absolutely nothing to do with insulin, so it

9   doesn't depend on insulin action in any way, and I

10   find that very attractive. And last but not least,

11   it actually produces some weight loss, which is, in

12   counter-distinction to so many of the other

13   diabetes drugs, which produce weight gain.

14   The safety issues I think are of some

15   concern, but I'm satisfied that the post-marketing

16   study will settle some of those issues. I agree

17   with Dr. Thomas, and Dr. Piantadosi, and Dr. Kaul

18   that there are some things we cannot learn -- there

19   are some things you just can't learn from clinical

20   trials. There's a limit to what we can do.

21   Eventually, in order to take medicine forward and

22   introduce innovative new things, we do have to make

1   decisions that imply some degree of risk.

2   Finally, I compliment the sponsors on their

3   courage in bringing this drug forward to this

4   particular committee and to the FDA. I feel like

5   I'm on the losing side yet again. And my

6   compliments to the FDA presenters and to the

7   company presenters, a very fine job.

8   DR. THOMAS: Any comments from the FDA?

9   DR. PARKS: Yes. On behalf of the FDA, I

10   would like to thank the advisory committee panel

11   members. Clearly, from today's vote, but more

12   importantly from the discussions from each member,

13   as you discussed how you came to your vote, you

14   have highlighted the difficulty of the benefit-risk

15   decision.

16   That burden is now going to fall upon us to

17   take into consideration all of the discussions that

18   have taken place today. You have clearly

19   identified a lot of areas that require additional

20   analyses. You've also suggested some very

21   important additional studies that could be

22   conducted, should be conducted. And so we will

1   seriously take this into consideration over the

2   next couple of months.

3   So, again, I would like to thank the panel

4   members, Dr. Thomas for doing an excellent job

5   chairing, Mr. Paul Tran, Dr. Paul Tran for also

6   assisting the division in preparing for this

7   advisory committee. I'd like to thank the FDA

8   review team, those who presented and also those who

9   assisted in all the presenters. And then, finally,

10   I would like to thank the sponsor, Bristol-Myers

11   Squibb and AstraZeneca, for an excellent

12   presentation and also their collegial working

13   relationship with the agency.

14   **Adjournment**

15   DR. THOMAS: So to conclude this meeting,

16   I'd like to thank the sponsors and the FDA for

17   their excellent presentations, the open public

18   hearing speakers for their presentations, the panel

19   for their excellent questions and discussion, and

20   the audience for paying attention and providing

21   good decorum.

22   So this meeting is concluded. Thank you.

1   (Whereupon, at 4:37 p.m., the meeting was

2   adjourned.)

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